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THE FDA'S GLP OUTLOOK DOCKET

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ABSTRACT

The GLP (Good Laboratory Practice) inspection procedures and the statistical evaluation of the complete inspections, one must still ask "How have the GLP inspections impacted new drug evaluation?". First, the people responsible for FDA's (Food and Drug Administration) bioresearch monitoring program are encouraged by the results of the GLP inspection seen in terms of industry's growing acceptance of the GLPs as a means of establishing a level of reliability for scientific testing. Furthermore, it is know that the deficiencies found by our inspection in the past year are not as severe as in recent years and the cooperation we are now receiving from laboratories during the investigations is at a higher level. Finally, and most important, the pharmacologists at the agency, particularly those who are keenly aware of the conditions that existed before the GLP regulations came into effect, are in agreement that the GLPs have made the reviewer's tasks much easier, and they, the reviewers, feel more confident of the reliability of the information that comesacross their desks.

PURPOSE

FDA to assure that all regulated products, including food and color additives, animal food additives, human and veterinary drugs, medical devices f o r human use, biological products and electronic products, are safe and effective for their intended use. Further to this end, FDA requires that all non-clinical toxicity studies be conducted under conditions that assure that the resultant final report is suitable for informed regulatory decision making. The agency believes

that this requirement can be met if the toxicology laboratory is operating in accord with universally accepted principles of good laboratory practices.

Figure 1 graphically represents the centers organized by the office of the associate commissioner for regulatory affairs.

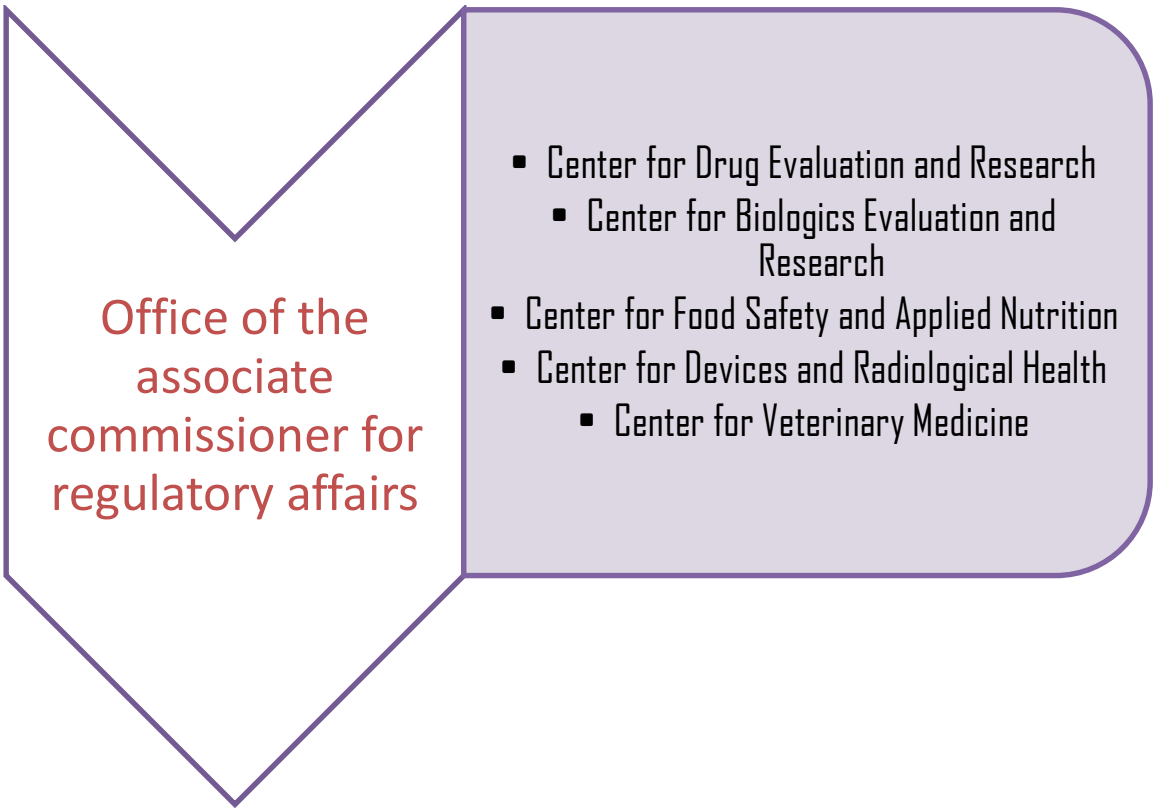

Fig. 1: Centers organized by the office of the associate commissioner for regulatory affairs

OBJECTIVES OF GLP REGULATIONS

The objectives of this program are: to inspect nonclinical laboratories engaging in studies that are intended to support applications [1] for research or marketing permits for regulated products to determine the degree of their compliance with the GLP regulations; to audit ongoing and completed nonclinical toxicity studies to verify their integrity and validity and to initiate appropriate corrective actions when GLP violations are encountered. The details of the program are contained in the FDA compliance program 7348.808.

TYPES OF GLP INSPECTIONS

There are two types of GLP inspections. The first is the routine inspection, a periodic evaluation of a laboratory's compliance with the GLP regulations. To facilitate scheduling of routine inspections, the agency maintains a list of nonclinical testing laboratories actively engaged in the toxicity testing of regulated products. These laboratories are inspected for GLP compliance at least once every 2 years. The GLP master schedule must list all of the studies

conducted at the laboratory that are subject to the GLP regulations. This master schedule, indexed by the test article must describe the test system, the nature of the study, the date the study was initiated, the current status of each study, the identity of the sponsor, and the name of the study director. Using the GLP master schedule sheet, the field investigator may exercise the option to select a study or studies that another of the FDA centers is required to evaluate for scientific content, rather than the studies designated by the center assigning the inspection [1, 2]. For example, if a testing facility to be inspected does not have an ongoing drug study, then a food additive, a veterinary drug, a medical device, or a radiation- emitting product safety study could be selected for audit. In such instances, the GLP staff for the assigning center forwards the information concerning the audited study to the appropriate center's GLP component for review and follow-up action.

The second type of GLP inspection is the directed, or for cause, inspection. The directed investigation is more complicated by its nature than the routine and is less frequently performed in the GLP program. These constitute only about 20% of the GLP investigations completed since the regulations were invoked. Directed inspections are assigned for one or more of the following reasons:

1. To determine if appropriate actions have been taken by a firm to correct serious GLP deficiencies noted in a routine inspection. This is normally done 6 months after the FDA receives the firm's assertions that corrections have been made.
2. To resolve concerns raised in the preclearance review of final study reports submitted to research or marketing permits, such as an Investigational New Drug (IND) application or a New Drug Application (NDA).
3. To validate critical studies, such as long-term and reproduction toxicity studies, submitted to INDs or NDAs. These studies are selected at each center from master schedules collected in the course of previous GLP inspections or from reviews prepared by the pharmacologist responsible for evaluating applications for research and marketing permits.
4. To verify validations performed by a third party for the sponsor.
5. To investigate seemingly questionable circumstances brought to the FDA's attention by other sources, such as the news media, other operating firms or laboratories, or disgruntled employees.

WORKING FACETS

Usually, investigators perform routine investigations alone. Headquarters' personnel, such as representatives of the Office of Regional Operations (ORO) and the Office of Enforcement, pharmacologists of the GLP staff of the assigning center, and on occasion, scientists from the reviewing divisions may be asked by the assigning Center to participate in the GLP investigations [3]. The ORO acts as a contact for the arrangements involving headquarters' participation in the inspection. The field investigator, designated as the team leader, has the responsibility for the conduct of the inspection and the preparation of the inspection report, known officially as the Establishment Inspection Report (EIR). Another

important preliminary to the inspection is the reinspection conference that is usually arranged to include all members of the inspection team as well as any other field and headquarters' specialists judged appropriate by the FDA center assigning the inspection.

EXPERT TO EXAMINE

The FDA can only enforce inspection of laboratories that perform tests on food, drugs, new animal drugs, or medical device products. Should a laboratory assumed to be doing nonclinical toxicity studies refuse to permit inspection, the laboratory will be advised by the FDA investigator that it is the policy of the agency not to accept studies submitted in support of any research or marketing permit if the agency does not have inspectional information regarding the GLP compliance status of the firm. Refusal to permit access to copying the master schedule sheet and its code sheets, Standard Operating Procedures (SOPs), and other documents pertaining to the inspection, are treated in the same way as a total refusal to permit inspection.

ELEMENTS OF A SURVEILLANCE INSPECTION

The first part of the surveillance inspection covers organization and personnel. Investigators must determine whether or not the facility has an adequate number of qualified personnel to perform hathe types and numbers of nonclinical laboratory studies [4]. FDA investigators describe in the EIRs the organizational structure and competency of the laboratory. To do this, FDA obtains an organizational chart and the summaries of the training and experience of the managers, study directors, and other appropriate supervisory personnel.

If personnel are involved in studies in a location other than that of the inspected facility, the sites and the personnel so involved must be identified. In fact, if there is a need for an inspection of the outside contract facility, this must be specifically noted in the EIR. As part of this evaluation, FDA must identify, through reviewing the facility personnel SOPs, how the facility recognizes and deals with health problems of the employees, especially those problems that may affect the quality and integrity of studies being performed by that individual. The Quality Assurance Unit (QAU), by evaluating QAU activities, the agency is able to assess the mechanisms by which the facility management assures itself that the nonclinical laboratory studies are conducted in a manner that will assure the quality and integrity of the data generated in the laboratory. This is most commonly accomplished by obtaining a list of the QAU personnel and the written procedures for QAU study audits and in-process inspections. The master schedule is also an important tool in the assessment of QAU activities. With it, the investigator can determine whether or not the QAU adequately maintains master schedule sheets and protocols with any subsequent changes or amendments. FDA investigators should always obtain copies of master schedule sheets dating from the last GLP inspection or covering at least the last 2 years.

The inspector must determine whether or not the facilities are of adequate size and design for completed or in-process studies. The physical parameters and systems of the facilities as they are used to accommodate the various operations employed in the GLP studies are examined.

Investigators also deal explicitly with the environmental control and monitoring procedures for critical areas, especially the rooms used for animal housing, the test a [4, 5] article storage areas, and the laboratory areas in which biohazardous material is handled. The procedures and methods for cleaning equipment and areas critical to study conduct as well as the current status of cleanliness are also closely examined. It must be determined that separate areas are maintained in rooms in which two or more functions requiring separation are per formed, as well as how that separation is controlled and maintained. This is done by examining the general condition, cleanliness, and ease of maintenance of the equipment in the various parts of the laboratory. Also, it must be determined that the equipment is located where it is to be used, and if necessary, located in a controlled environment. For representative pieces of equipment, the investigators check for SOPs, maintenance schedules and logs, and standardization and calibration procedures. It also must be determined if standards for calibration and standardization are available. Investigators must be aware of any equipment deficiencies that might result in contamination of test articles, uncontrolled stress to the test system, and erroneous test results. Investigators also learn if the same equipment is used to mix test and control articles, and if so, whether the procedures are adequate to prevent cross-contamination.

They must judge whether the studies are being conducted in conformation with these SOPs and in a manner designed to assure the quality and integrity of the data. To accomplish this, they obtain copies of the index and representative samples of all of the laboratory's written SOPs. Furthermore, these SOPs must be available at the locations at which they are to be used. All SOPs and any changes to the SOPs must be appropriately authorized and dated and historical files of SOPs must be maintained. The procedures for familiarizing employees with SOPs must also be reviewed.

Animal care and housing must be adequate to prevent stress and uncontrolled influences that could alter the response of test systems to test articles. The personnel responsible for receiving and examining animals are evaluated along with the animal care procedures, including any routine treatments, such as vaccination and deworming. Further, FDA ex amines the criteria used to determine when and for how long animals should be kept in quarantine. Relative to this, GLPs used to separate species and the methods used in handlingor isolating diseased animals are examined

The FDA reviews the procedures used to ensure that the identity and the dose of test articles administered to the test systems is known and is as specified in the study protocol. In the course of assessing this, the investigators evaluate the methods used in the acquisition, receipt, and storage of test articles. Also, that means used to prevent deterioration and contamination must be evaluated. The identification, homogeneity, potency, and stability of the test articles and the means used to determine these parameters are also closely examined. The methods used to ensure test article integrity and accountability and for retaining and retesting reserve samples of test and control articles must also be evaluated.

PREPARATION OF THE EIR

The lead investigator is responsible for the

preparation of the EIR. Other members of the inspection team may be called upon to participate in its preparation, however, particularly in supplying specialized scientific or technical information [5, 6]. The field investigator and the supervisor at the district office will tentatively classify the completed EIR under one of the following three categories: No Action Indicated (NAI), Voluntary Action Indicated (VAI), or Official Action Indicated (OAI).

CONCLUSION

Before concluding a GLP inspection, FDA officials meet with appropriate laboratory personnel to discuss any observed deviations from GLPs. If there are no departures from the GLP regulations, the facility representatives are so informed during the exit interview and no documentation is given to the firm. If significant deficiencies are found, the laboratory will be presented with a form FDA Inspectional Observations. This form lists the deviations from the GLP regulationsas observed by the FDA investigational team during the inspection. When the FDA 483 is issued during the exit interview, the representatives of the laboratory have an opportunity to discuss the statements made therein. The forms may be altered or changed as a result of the exit interview discussions. When issued at the end of the on-site phase of the inspection, the final version of the FDA 483 becomes immediately available under the Freedom of Information Act. As in every inspection performed under the auspices of the act, an EIR reflecting all the findings and discussions is prepared by the lead investigator.

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