The Good Laboratory Practices (GLPs) are extremely effective guidelines intended to provide management with a tool for controlling regulated laboratories and to provide regulators with a measurement guide for the evaluation of those controlling efforts. Over the past decade the GLPs have survived the test of field scrutiny and have evolved into a meaningful set of standards for a variety of laboratories worldwide.

The effects of evolution on regulation are generally positive. Vague requirements are clarified with example, dispute resolution, and dissemination of interpretation. Differences of opinion are debated, discussed, and synthesized. Guidelines are issued, investigators are trained, and examples are provided.

Working in conjunction with this delineation of regulation are the variances created by changes in practice, technology, and focus. The conjunction of these forces may create its own conflict, but experience and time have a soothing influence even on disagreement; positions and opinions may be at variance, but they are at least clear and specific.
The GLP regulations have reached this next stage of evolved understanding. The requirements are clear, the guidelines and interpretations are available, and the conflicts are resolved. Even the revolutionary influences of computerization in the laboratory have been measured and considered, providing the good automated laboratory practices corollary guidelines. The GLPs have come of age, and provide a clear and consistent framework for the assurance of quality and control in the laboratory.

This maturity has led to global GLPs that are, if not identical, at least compatible. In the United States, the same general guidelines apply to laboratories regulated by the Food and Drug Administration (FDA), Environmental Protection Agency (EPA) labs, and general analytical laboratories. Those same standards are consistent with required procedures in the European Community (EC); Switzerland, Japan, Israel, Brazil, and Russia. The Worldwide concern for quality and control had evolved the same general principles of operation and organization.

This third edition of Good Laboratory Practice Regulations reflects that evolutionary maturity of requirements. With a relative uniformity of interpretation more specific and applied information can be provided, furnishing the reader with both the theoretical overview necessary to anticipate new and emerging interpretations and the detail of practical information that can serve as a guide to the current standards and requirements of good laboratory management.

Chapter 1 provides a historical review of the evolutionary process, tracing the problems and concerns of regulators and the response of laboratory managers to those issues. The ultimate result, is the series of guidelines published as the GLPs, provided with a context and rationale.

Chapter 2 provides a definitive review of the current version of FDA GLPs, including an analysis and interpretation of the enforcement of the GLPs. This summary is an excellent
overview for readers not previously familiar with the requirements.

Chapter 3 examines the new FDA regulation, Part 11, and its impact on a GLP laboratory setting. This chapter argues that Part 11 is a de facto extension of the GLPs and represents a historical update of the GLP regulation.

Chapters 4 and 5 focus on two important applications of the GLPs. In Chapter 4 the GLPs are applied to an automated laboratory as the (EPA) good automated laboratory practices. Chapter 5 examines the impact and interpretation of the GLPs in a non-GLP analytical laboratory. Stephanie Olexa makes an impressive case that the GLPs are relevant guidelines even where they are not regulatory requirements.

Chapter 6 provides specific standards and general guidelines for the validation of Laboratory Information Management Systems (LIMS) and other computerized laboratory systems. The chapter includes specific interpretations of the validation requirements in the post-Part 11 environment.

A review of standards without an examination of the interpretation and enforcement of those standards would be of little value. In Chapter 7 therefore, the FDA's GLP inspection program is dissected and analyzed, revealing the philosophy and approach of the regulators to GLP field interpretation.

In each previous edition the eighth and final chapter has been dedicated to the art of prediction, providing an extrapolation of GLP trends and applications into the near-term future. These predictions have provided gratifyingly accurate recommendations for anticipating new regulatory and practical changes. In this third edition, Chapter 8 looks at the next step in laboratory automation: robotic control of samples and analysis, the field laboratory, new laboratory applications in DNA and other genetic testing, and emerging new government perspectives on regulation and enforcement.

These eight chapters provide a detailed review of the GLP requirements, an examination of the application of
those requirements, an interpretation of the effects of GLPs on an automated laboratory and the effects of that automation on the GLP guidelines, and a look at future trends in laboratories and their regulation.

Sandy Weinberg
Contents

Preface
Contributors

1. Historical Perspective
   Jean M. Taylor and Gary C. Stein

2. FDA/GLP Regulations
   Wendell A. Peterson

3. Applying 21 CFR Part 11 to the Laboratory Environment
   Sandy Weinberg

4. The Good Automated Laboratory Practices
   Gerald J. Whartenby, Paul L. Robinson, and Sandy Weinberg

5. Implementing GLPs in a Non-GLP Analytical Laboratory
   Stephanie A. Olexa

Copyright © 2003 Marcel Dekker, Inc.
6. **Computer Systems Validation**  
   *Sandy Weinberg*

7. **The FDA’s GLP Inspection Program**  
   *George W. James*

8. **The Future**  
   *Sandy Weinberg*

*Bibliography*
Contributors

George W. James  U.S. Food and Drug Administration, Rockville, Maryland, U.S.A.

Stephanie A. Olexa  Benchmark Analytics, Center Valley, Pennsylvania, U.S.A.

Wendell A. Peterson  Parke-Davis Pharmaceutical Research Division of Warner-Lambert Company, Ann Arbor, Michigan, U.S.A.

Paul L. Robinson  Muhlenberg College, Allentown, Pennsylvania, U.S.A.


Jean M. Taylor*  U.S. Food and Drug Administration, Rockville, Maryland, U.S.A.

Copyright © 2003 Marcel Dekker, Inc.
Historical Perspective

JEAN M. TAYLOR*
U.S. Food and Drug Administration, Rockville, Maryland, U.S.A.

GARY C. STEIN
Weinberg, Spelton & Sax, Inc., Boothwyn, Pennsylvania, U.S.A.

THE PROBLEM IN THE 1970s

FDA’s Perspective

The Federal Food, Drug and Cosmetic Act (FFDCA) places the responsibility for establishing the safety and efficacy of human and veterinary drugs and devices and the safety of food and color additives on the sponsor of the regulated product. The Public Health Service Act requires that a sponsor
establish the safety and efficacy of biological products. These laws place on the Food and Drug Administration (FDA) the responsibility for reviewing the sponsor’s test results and determining whether or not the results establish the safety and efficacy of the product. If the agency accepts that safety and efficacy are established adequately, the sponsor is permitted to market the product.

The types of scientific tests needed to establish safety are dependent on the nature of the regulated product and its proposed use. A product such as a food or color additive will require tests to elucidate the potential of the product to induce adverse acute, subchronic, and chronic effects. The safety tests are generally performed in animals and other biological systems. Both the types of tests and the methodology of particular tests have changed over the years with scientific advances in the field of toxicology.

The FDA regulations or guidelines prescribe the types of safety tests for a particular product. Sponsors may conduct the studies in their own laboratories or have them performed by a contract laboratory, a university, or some other type of laboratory. The sponsor submits the study reports to the FDA in food and color additive petitions, investigational new drug applications, new drug applications, new animal drug applications, biological product license applications, and other requests for permission to market a product.

Food and Drug Administration scientists evaluate the safety studies to determine whether or not the results support a conclusion that the product can be used safely. Until the mid-1970s, the underlying assumption in the agency review was that the reports submitted to the agency accurately described study conduct and precisely reported the study data. A suspicion that this assumption was mistaken was raised in the agency’s review of studies submitted by a major pharmaceutical manufacturer in support of new drug applications for two important therapeutic products. Review scientists observed data inconsistencies and evidence of unacceptable laboratory practices in the study reports.
The FDA’s Bureau of Drugs requested a “for-cause” inspection of the manufacturer’s laboratories to determine the cause and extent of the discrepancies. A for-cause inspection is one initiated at the request of an agency unit when there is reason to suspect a problem in an FDA-regulated product. The authority to make for-cause inspections is a general one under the FFDCA, but one that had rarely been applied to animal laboratories.

In a statement in a Senate hearing on July 10, 1975, Dr. Alexander M. Schmidt, commissioner of food and drugs, reported the preliminary results of further agency investigations [1]. The findings indicated defects in design, conduct, and reporting of animal studies. For-cause inspections were conducted at several laboratories and revealed similar problems. The nature and extent of the findings in these inspections raised questions about the validity of studies being submitted to the agency.

The deficiencies observed in these inspections were summarized in the preamble to the proposed good laboratory practice regulations [2] as follows:

1. Experiments were poorly conceived, carelessly executed, or inaccurately analyzed or reported.
2. Technical personnel were unaware of the importance of protocol adherence, accurate observations, accurate administration of test substance, and accurate record keeping and record transcription.
3. Management did not assure critical review of data or proper supervision of personnel.
4. Studies were impaired by protocol designs that did not allow the evaluation of all available data.
5. Assurance could not be given for the scientific qualifications and adequate training of personnel involved in the research study.
6. There was a disregard for the need to observe proper laboratory, animal care, and data management procedures.
7. Sponsors failed to monitor adequately the studies performed in whole or in part by contract testing laboratories.

8. Firms failed to verify the accuracy and completeness of scientific data in reports of nonclinical laboratory studies in a systematic manner before submission to the FDA.

The problems were so severe in Industrial Bio-Test Laboratories (IBT) and Biometric Testing Inc. that both laboratories ceased doing preclinical studies. Industrial Bio-Trust Laboratories had been one of the largest testing laboratories in the United States, with thousands of its studies serving to support the safety of drugs, pesticides, and food additives. The FDA and the Environmental Protection Agency (EPA) began reviewing all the compounds that relied on IBT and Biometric Testing Inc. studies for support of safety. The agencies required the study sponsors to submit outside audits of the study data. From the audits of the IBT studies, EPA found 594 of 801 key studies, or 85% to be invalid [3]. The FDA’s Bureau of Foods found 24 of 66 IBT studies, or 36% to be invalid [4].

Criminal charges of fraud were brought against four IBT officials. Three of the officials were convicted; a mistrial was declared in the case of the fourth official because of illness [5].

**FDA’s Response to the Problem**

The conclusion that many studies on which the safety of regulated products had been based could be invalid was alarming to the FDA, the EPA, Congress, the public, and industry. Commissioner Schmidt established the Bioresearch Monitoring Program in early 1976 to develop a program that would deal with the problem of data validity not only in the area of safety studies but also in clinical testing. Congress voted a
special appropriation of $16 million and additional personnel to support the program.

A steering committee, chaired by the associate commissioner for compliance and composed of the associate commissioners, the bureau directors, the chief counsel, the director of the National Center for Toxicological Research, and the executive director for regional operations, directed the program. Four task forces—the Toxicology Laboratory Monitoring Task Force, the Investigator Sponsor Task Force, the Institutional Review Committee Task Force, and the Administrative Task Force—handled different components of the program. The responsibility for developing a strategy to ensure the validity and reliability of all nonclinical laboratory studies to support the safety of FDA-regulated products was assigned to the Toxicology Monitoring Task Force. This task force was instructed to inventory all firms submitting research to the FDA and other involved federal agencies; to develop formal agreements with other agencies for the inspection of laboratories; to develop and publish standards for measuring the performance of research laboratories; to develop agencywide enforcement strategies; and to develop plans for hiring, training, and assigning the new employees authorized by Congress for the program.

The Toxicology Monitoring Task Force chose the publication of GLP regulations as the best approach for assuring study validity. Six other approaches were considered but were discounted as not feasible or efficient.

- One approach would have been to continue the program of for-cause inspections, but they would be triggered only by perceived deficiencies in the data after submission to the agency, and thus would not have provided systematic assurance that all studies were valid or guidance to laboratories on standards for conduct of studies.
- A second approach would have been to shift responsibility for nonclinical testing of regulated products to
the FDA. Such a shift would have required congressional authorization, because the FFDCA clearly places this responsibility on the sponsor of the product. In addition, the costs of such a shift would have been prohibitive.

- The third approach considered was for the agency to publish detailed test protocols and procedures for studies on regulated products. This, however, would have discouraged the use of informed scientific judgment in designing tests and inhibited the development of new toxicological methods.

- Another approach would have been to establish licensing procedures for testing laboratories, but developing uniform licensing criteria would have been very difficult, considering the variety of regulated products, test types, and laboratory facilities.

- Still another approach was the establishment of a full-time, on-site inspection program for laboratories similar to the U.S. Department of Agriculture’s inspections of meat-processing plants. Such a program was considered to be an inefficient use of the FDA’s investigational resources, because many testing facilities are too small or too diversified to justify full-time, on-site monitoring.

- Consideration was also given to the publication of GLP guidelines rather than regulations. While this would have provided the testing facilities with standards of conduct, it would not have given the agency an enforcement mechanism to ensure that the standards were met.

The regulations approach had several advantages. It was within the legal mandates of the agency and allowed efficient use of agency resources for ensuring compliance. It was also similar to the use of good manufacturing practice (GMP) regulations with which most of the regulated industries were already familiar. The main advantage, however, was that the
regulations approach focused on the process by which testing facilities carried out studies rather than on the product being tested or the studies themselves. The use of scientific judgment in the planning and conduct of safety studies thus was not hampered, and the detail required for a focus on specific studies, or kinds of studies, was avoided.

Once the decision to establish GLP regulations had been made, a subcommittee was appointed to draft the regulations. This subcommittee was composed of individuals representing all the FDA bureaus and a variety of scientific disciplines. The subcommittee began its work with a rough draft that had already been prepared by personnel in the Bureau of Drugs. This early draft had used two independent, unsolicited sets of GLP guidelines submitted by G. D. Searle and Co. and the Pharmaceutical Manufacturers Association. The subcommittee’s first draft was circulated to all FDA bureaus for comment, revised on the basis of these comments, and then circulated to other government agencies for comment. The subcommittee considered these comments in preparing the final draft, which was published as the proposed GLP regulations on November 19, 1976. The proposed regulations were designated as a new part 3.e. of Chapter 21 of the Code of Federal Regulations, but the final regulations were codified as part 58 (21 CFR Part 58).

**FDA’S PROPOSED REGULATIONS**

The purpose of the GLP regulations is to assure the quality and integrity of the data submitted to the FDA in support of the safety of regulated products. To this end, most of the requirements of the proposal would have been considered familiar and reasonable by any conscientious scientist. Protocols and standard operating procedures (SOPs), adequate facilities and equipment, full identification of test substances, proper animal care, equipment maintenance, accurate recording of observations, and accurate reporting of results are
basic necessities for the conduct of a high-quality, valid toxicity, or any scientific study. The proposed regulations also placed a heavy emphasis on data recording and record and specimen retention to ensure that a study could be reconstructed at a later time if the need arose.

The proposed regulations went beyond these basic requirements for a valid study by requiring each study to have a study director who would have “ultimate responsibility for implementation of the protocol and conduct of the study” [§ 3e/31(a)], and each testing facility to have a quality assurance unit to monitor conduct of studies. The concept of a quality assurance unit to monitor study conduct was a new one to most laboratories but a familiar one in manufacturing facilities operating under various GMP regulations.

In addition, because the GLPs were regulations, the proposal identified the scope of the regulations, the authority under which they were promulgated, and the strategy for their enforcement.

Scope

The Toxicology Monitoring Task Force had not specified what types of studies would be considered to be within the scope of the GLPs. The subcommittee that drafted the regulations defined a nonclinical laboratory study as “any in vivo or in vitro experiment in which a test substance is studied prospectively in a test system under laboratory conditions to determine its safety” [§ 3e.3(d)]. The proposal explained that the term was to include only those studies conducted for submission to the FDA in support of an “application for a research or marketing permit.” This latter term was a means of referring to the numerous categories of data required to be submitted to the agency, such as food and color additive petitions, new drug applications, and new animal drug applications. The studies covered by the regulations included all kinds of toxicity studies—from in vitro mutagenicity studies to acute, subchronic, and long-term toxicity/carcinogenicity
studies—in which inadequate effectiveness might affect safety. Studies excluded from the scope of the regulations were those utilizing human subjects, clinical studies or field trials in animals, basic exploratory studies, or studies to determine physical or chemical properties of a test substance independent of a test system.

The proposal recognized that the scope might justifiably be defined on a different basis, possibly on a facilities basis, and asked for comments on whether specific types of testing facilities might be excluded from coverage by the regulations.

Enforcement Strategy

The basic mechanism of enforcement was to be inspection of testing facilities by FDA field investigators. The FDA’s authority to conduct inspections of facilities engaged in interstate commerce of regulated products is well established, and such inspections are the primary method of enforcement of the FFDCA. Under the proposal, studies performed by a testing facility that refused to permit inspection would not be accepted in support of an application for a research or marketing permit.

At the conclusion of an inspection, the FDA investigator notifies the facility of any deficiencies identified during the inspection, both in writing (on Form 483, “Notice of Inspectionsal Observations”) and in discussion with management. If the deficiencies were of a kind that might affect study validity, more formal warnings would be issued to the testing facility through a regulatory letter or a notice of adverse findings.

Initial planning under the Bioresearch Monitoring Program called for each testing facility to be inspected yearly. It was later decided that a biennial inspection would suffice to ensure that all 2-year studies would be inspected at least once while in progress.

When deficiencies were extensive enough to affect the validity of a study, the proposal provided that the study
would not be considered by the FDA in support of a research or marketing permit. The proposal noted that the data from such a study had to be submitted to the agency, however, and that if they were adverse to the product might still be used as a basis for regulatory action. This difference in treatment was justified by the consideration that a bad study might reveal an adverse effect but could not establish the absence of an adverse effect.

The final and most severe enforcement strategy under the proposal was the disqualification of a testing facility. Data from a disqualified facility would not be accepted in support of a research or marketing permit. The agency viewed this penalty as one that would only be employed in cases in which the testing facility had severe, widespread deficiencies that raised questions about the validity of all the studies performed in the facility and in which previous regulatory efforts had failed to bring the facility into compliance with the regulations. Unlike the other enforcement strategies, there was no specific authority for disqualification; the GLP regulations themselves established this authority.

Authority

The GLP regulations were issued under the general mandate of section 701(a) of the FFDCA, which empowers the commissioner to promulgate regulations for the efficient enforcement of the act. The commissioner's power to issue regulations for determining that a clinical investigation of a drug intended for human use be scientifically reliable and valid [21 CFR 314.111(a)(5)] had been upheld by the Supreme Court in the decision Weinberger v. Hynson, Westcott and Dunning, Inc., 412 U.S. 609 (1973). The clinical investigations regulations had also been issued under section 701(a) of the FFDCA. It was further considered that the authority to issue GLP regulations gave the agency the authority to establish the terms on which it would accept nonclinical testing data; therefore the proposed regulations provided for the rejection of studies.
if the testing facilities refused to permit inspection. The FDA already had the authority to compel inspection of nonclinical laboratories doing work on new drugs, new animal drugs, or medical devices. The FDA may inspect both manufacturing establishments and laboratories concerned with drugs and devices and examine research data on these products under section 704(a) of the FFDCA.

COMMENTS ON THE PROPOSAL AND THE FINAL REGULATIONS

More than 1000 individual items were contained in 22 oral responses from a 2-day public hearing and 174 written responses to the proposal. Many responses commented on both general issues, such as scope, and specific details in individual sections and paragraphs. The preamble to the final regulations addressed these comments in detail, and modifications, both substantial and editorial, were included in the final regulations, which were issued on December 22, 1978, and became effective June 20, 1979 [6].

Management and the Study Director

As outlined in the proposal, comments on the responsibilities of the study director identified many of these responsibilities as the prerogative of management. In response to these comments, a new section (§ 58.31) was included in the final regulations. This section established that if necessary, the management of the testing facility had the responsibility for designating and replacing the study director; for providing a quality assurance unit and assuring the actions to correct deviations reported by the quality assurance unit are taken; for assuring that the personnel and the tools (e.g., facilities and equipment) are available as needed; and for assuring that test and control articles are appropriately identified.

Despite making management responsible for many areas that the proposal had assigned to the study director, the
final regulations retained the concept of the study director as the single focus of responsibility for study conduct by redefining the function of the study director as “overall responsibility for the technical conduct of the study, as well as for the interpretation, analysis, documentation and reporting of results, and represents the single point of study control” (§ 58.33).

The Quality Assurance Unit

Not surprisingly, many comments objected to the requirement for a quality assurance unit on the basis of increased costs, administrative burden, and interference with management prerogatives and informed scientific judgment of study directors. An alternative solution for study monitoring was not suggested, however.

The FDA retained the requirement for a quality assurance unit, or function, to monitor studies for conformance to the regulations. It was emphasized that the function was administrative rather than scientific. The personnel responsible for quality assurance for a given study were required to be separate from, and independent of, the personnel responsible for the direction and conduct of that study.

Many commentators wanted the inspection records compiled by the quality assurance unit excluded from the records to be inspected by the agency on the basis that an inspection “might violate the constitutional privilege against compelled self-incrimination.” The agency rejected this argument, because the privilege against compelled self-incrimination is not available to a collective entity, such as a business enterprise, or to an individual acting as a representative of a collective entity. The agency did, however, exclude the quality assurance unit’s inspection records form inspection to encourage more forthrightness in the reports. The quality assurance unit was required to certify that the inspection of studies and final reports had been made by means of a signed statement to be included in the final report [§ 58.35(b)(7)].
Scope

In general, the comments on the proposed regulations sought limitations through exclusion of various classes of FDA-regulated products, such as medical devices; various types of facilities, such as academic and not-for-profit organizations; or various types of studies, such as short-term studies. These suggestions were rejected primarily because the basic purpose of the regulations—to ensure the validity of safety data submitted to the agency—would have been frustrated by excluding particular products, facilities, or studies from coverage. None of the commentators suggested an alternative overall approach to defining the scope of the regulations.

The scope adopted in the final regulations was only slightly changed from the proposal; the main difference was the exclusion of functionality studies from coverage.

Inspections

The major concerns of the commentators with respect to the actual inspection of facilities were the competence and scientific qualifications of the FDA investigators. In early inspections (both the for-cause inspections prior to the proposal and the inspections made in the pilot program under the proposal), the agency assigned its most experienced field investigators and sent agency scientists to participate in the inspections. To further assure the competence of the investigators, a training program was established at the National Center for Toxicological Research for both field investigators and scientists. The compliance program for the GLPs also provides for scientific review in FDA headquarters of all GLP inspection reports.

That testing facilities still doubt the competence of some field investigators was evident in a comment on the 1987 revision of the GLPs [7], which requested training in the GLPs for the FDA’s field personnel.
Disqualification

Numerous comments were made on the provisions for disqualification of a testing facility (subpart K). Although the proposal stated that the agency considered that it would only rarely invoke this penalty, it appeared from the objections that industry had interpreted these provisions to mean the agency would invoke disqualification frequently and for minor failures to comply with the regulations. On the basis of the objections, the sections of subpart K on purpose (§ 58.200) and the grounds for disqualification (§ 58.202) were extensively revised. The revision stated that the purposes of disqualification were as follows:

1. To permit the exclusion of completed studies from consideration in safety evaluation until it could be shown that noncompliance with the regulations did not affect the validity of the study data
2. To permit the exclusion of studies completed after disqualification from consideration in safety evaluation until the facility could demonstrate that it would conduct studies in compliance with the regulations.

Three grounds for disqualification were given in the final regulations; all three must be present to justify disqualification.

1. Failure of the facility to comply with one or more of the GLP regulations or other regulations applying to facilities published in Chapter 21 of the Code of Federal Regulations
2. Adverse affects on the validity of the studies
3. Failure to achieve compliance with regard to lesser regulatory actions, such as warnings or rejection of studies

EVALUATION OF THE FDA PROGRAM

The proposed GLP regulations announced that based on the requirements of the proposal, the FDA would conduct a number of surveillance inspections of testing facilities during No-
November and December of 1976 and January of 1977. These inspections had the dual purpose of determining the status of the laboratories and evaluating the work ability of the proposed regulations. The results of this pilot inspection program were analyzed and published by the FDA’s Office of Planning and Evaluation [8].

Forty-two laboratories were identified for inspection. Ongoing and completed studies would be examined as available. The inspections used a checklist that was divided into two parts, one part covering laboratory operations and the other study conduct. The checklist arbitrarily placed mixing and storing of test substances in the area of laboratory operations and distribution and characterization of the substances in study conduct.

In the completed survey, only 39 laboratories, with 67 studies, yielded usable data. Twenty-three of the testing facilities were sponsor laboratories, 11 contract laboratories, and five university laboratories. Forty-eight of the studies were completed and 19 ongoing. The findings showed that sponsor laboratories met 69% of the requirements, the contract laboratories met 56% of the requirements, and university laboratories met only 46% of the requirements.

Requirements in the areas of facilities, animal care, and personnel were the most often met, while the fewest requirements were met in the areas of the quality assurance unit, mixing and storage of the test substances, and record retention.

Ongoing studies showed better adherence (73% of the requirements met) than did completed studies (57%). Animal care and test substance distribution showed the greatest degree of adherence. Low degrees of adherence were found in the quality assurance function and protocol-related requirements. The comments of the agency investigators indicated that testing facilities were already making changes in their ongoing studies to bring them into compliance.

Following publication of the final regulations, a second survey was conducted to measure compliance against the final requirements [9]. The study sample consisted of 17 spon-
sor laboratories, 10 contract laboratories, and one university laboratory. The average compliance rate was 88%, with the deficiencies observed in sponsor and contract laboratories showing little difference. Compliance was measured both by the average compliance rate with the requirements of a section of the regulations or by the number of laboratories failing to meet one or more of the section's requirements. The following sections showed high compliance by both measurements: personnel, management, study director, general facilities, and facilities for animal care, handling of test and control articles, laboratory operations, specimen and data storage, record retention, and personnel and administration. Areas that showed low compliance by the same measures were quality assurance units, maintenance and calibration of equipment, SOPs, animal care (primarily the failure to analyze feed and water for interfering contaminants), test and control article characterization, mixtures of articles with carriers, study protocol, and study conduct (primarily failure to sign and date data sheets or to follow the protocol).

The results of these surveys indicated both the practicality of the regulations and the success of the vigorous efforts that most testing facilities were making to achieve compliance. The record of compliance continued to be good. In its 1984 update of compliance results [10], the FDA reported that 72% of the inspection reports since 1976 showed few or no substantial deviations from the regulations and 23% showed minor to significant deviations that could be corrected voluntarily by the testing facility. Four percent of the reports, however, showed significant deviations requiring corrective action within a specified period of time, and studies are still occasionally rejected because significant deviations render them invalid.

THE PROBLEM FROM EPA'S PERSPECTIVE

The EPA had concerns similar to those of the FDA. Under section 4 of the Toxic Substances Control Act (TSCA), the EPA evaluates laboratory data submitted to the agency re-
garding tests of the health effects of chemical substances and mixtures. Also, under authority of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), the EPA evaluates laboratory test data relating to hazards to humans arising from the use of a pesticide product when the agency evaluates pesticide registration applications.

The EPA was aware of the problems the FDA had uncovered in the mid-1970s relating to unacceptable laboratory practices. The EPA responded to the FDA's findings by forming the toxicology auditing program in the agency's Office of Pesticide Programs. The EPA also held public hearings to solicit comments on how appropriate the agency's approach was to data quality assurance for pesticide testing.

In 1978, the EPA and FDA formalized both agencies' commitment to establish a coordinated quality assurance program through an interagency agreement. Under this agreement, the FDA provided assistance during EPA data audits. Between 1978 and 1979, the agencies performed 65 joint audits that indicated that some testing facilities did not follow GLPs. The EPA referred some of these facilities to the Department of Justice for prosecution.

**EPA'S PROPOSED REGULATIONS**

Like the FDA, the EPA considered different approaches to assure that data submitted to the agency complied with necessary quality standards.

Licensing or certification of laboratories was considered impractical for toxicology laboratories because of the great diversity and range of testing capabilities and the complex quality control procedures used in toxicology testing.

A voluntary standard-setting scheme administered by the private sector was rejected because such schemes were considered practically unenforceable.

Like the FDA, the EPA determined that the promulgation of GLP regulations would most effectively handle the
problem of compliance with adequate control standards, and the agency published proposed health effects standards for testing under TSCA on May 9, 1979 [11]. Proposed GLP regulations applicable to laboratory studies submitted to the EPA in compliance with FIFRA were published on April 18, 1980 [12]. Supplemental GLP standards for the development of data on physical, chemical, persistence, and ecological effects of chemical substances for which the EPA requires testing under section 4 of TSCA were published on November 21, 1980 [13]. The EPA took this action because the previously published GLPs for health effects testing did not address the analytical problems associated with physical, chemical, and persistence testing.

Differences Between EPA Proposed Regulations and FDA Regulations

When it issued proposed GLP regulations in 1978 and 1980, the EPA harmonized those regulations that the final GLP regulations which had been issued by the FDA in 1978. There were major differences, however, because the two agencies’ approaches to regulating laboratory studies differed. The specific working of various sections of the EPA’s proposed regulations varied from those of the FDA because of the differing scope of the authority of each agency.

EPA’s Final Regulations

The EPA’s FIFRA and TSCA GLP regulations were both issued in final form on November 29, 1983 [14]. The FIFRA GLP regulations were codified as 40 CFR 160, and the TSCA GLP regulations as 40 CFR 792. In terms of the TSCA GLPs, the final regulations incorporated the proposed GLPs issued on May 9, 1979 and November 21, 1980.

GLP REVISIONS IN THE 1980S

FDA Revisions

In 1984, the FDA proposed revising its 1978 GLP regulations. The rationale for this revision was to clarify, amend, or delete
provisions of the regulations in order to reduce the regulatory burden on testing facilities.

During agency inspections, the FDA had found that most laboratories were complying with the GLP requirements—indeed, that the violations it had noted in the mid-1970s were the exception, rather than the general rule—and the agency thought that it could streamline the regulations without compromising the GLP program. The FDA had also received comments and questions about the GLP regulations that indicated that several GLP provisions did not significantly contribute to the quality and integrity of data submitted to the agency. At the same time, the agency was undertaking a review of its regulations to minimize regulatory burdens.

The FDA established a GLP review task team to identify provisions in the regulations that could be amended or deleted, and this team recommended revisions to 36 GLP provisions. Recommendations were issued as a proposed rule on October 29, 1984 [15]. The proposal made various changes to definitions to reduce the amount of paperwork required for nonclinical laboratory studies and to clarify earlier GLP provisions. Similar clarifications were made to the provisions, delineating the definition and function of the study director and quality assurance unit.

In the 1984 proposal, changes were also made to inform collection requirements subject to the Paperwork Reduction Act of 1980. Modifications were made to the provisions regarding animal care, animal supply, and administrative and personnel facilities. Provisions regarding equipment design, maintenance and calibration of equipment, SOPs, animal care, test and control article characterizations, and mixtures of articles with carriers were changed to allow more flexibility of laboratory operations. The section on laboratory protocols was amended to eliminate unnecessary entries by allowing laboratories to identify the information applicable to the articles being tested. The agency also deleted the requirements that the selection of the test system be justified in the protocol. Other changes to the GLP regulations involved revi-
sions to provisions regulating conduct of laboratory studies and the storage, retrieval, and retention of records.

The FDA received 33 comments on its proposed GLP revisions. After considering these comments, the agency issued its final GLP provisions on September 4, 1987 [16]. Some of the comments received by the agency indicated a need to add new terms to the definition section of the regulations (e.g., study initiation and study completion), while others encouraged the FDA to retain the original GLP language in certain provisions rather than make the amendments the agency had proposed in 1984.

**EPA Revisions**

Among the comments received by the FDA, eight comments urged the agency to encourage the EPA to adopt similar revisions to its GLP regulations, which were now more stringent than the FDA’s regulations. The FDA stated that the agency consulted with the EPA regarding the changes made to the FDA’s regulations, and that the FDA would cooperate with the EPA when the latter agency revised its own GLP regulations. As a result of its own monitoring of GLP compliance, EPA agreed that its own GLP regulations could be streamlined without compromising the integrity of data submitted to the agency.

The EPA’s proposed revisions to its FIFRA and TSCA GLP regulations were issued on December 28, 1987 [17]. The EPA agreed with the FDA that many GLP provisions could be amended to incorporate the changes that had been made by the FDA. In addition, the scope of the FIFRA regulations was expanded to include environmental testing provisions that already existed in the TSCA GLPs, and to include product performance data (efficacy testing). The EPA also proposed changes. Some changes were made to the proposed regulations in response to these comments, such as exempting from routine EPA inspections the records of quality assurance unit findings and problems, as well as records of correc-
tive actions recommenced and taken, except under special circumstances. The final versions of EPA’s revisions to its GLPs were issued on August 18, 1989 [18].

The EPA’s proposed GLP revisions basically conformed to the charges the FDA had made in the latter agency’s final rule of September 4, 1987. The major differences between the EPA proposals and the FDA GLPs continued to reflect the varying needs and responsibilities of each agency and the expanded scope of the EPA’s regulations in light of the testing and test systems affected under the EPA’s authority to require test data in support of research or marketing permits to include ecological effects, environmental and chemical fate, and efficacy testing in addition to health effects testing.

Other federal agencies, as well as international agencies and organizations, also developed GLP programs. The National Toxicology Program concluded that studies performed under contract to the program should be performed in compliance with GLPs, and established a quality assurance function to monitor the laboratories and studies. In 1981, the Organization for Economic Cooperation and Development (OECD) developed GLP principles for studies performed for the European Economic Community (EC) countries. Between 1986 and 1988, EC council directives adopted the OECD and required that all EC countries monitor and verify compliance with those standards.

In 1982, the Japanese Ministry of Health and Welfare issued GLP standards for safety studies on drugs. This was followed in 1984 by GLP standards issued for studies on industrial chemicals by the Japanese Ministry of International Trade and Industry and GLP standards for toxicological studies on agricultural chemicals by the Japanese Ministry of Agriculture, Forestry, and Fisheries. There are differences in these regulations and guidelines that pose problems for sponsors planning studies to meet the requirements of different agencies or countries [19].

As a solution to part of this problem, the FDA has developed memoranda of understanding (MOUs) with Canada
(1979), Sweden (1979), Switzerland (1985), France (1986), Italy (1988), Germany (1988), the Netherlands (1988), and the United Kingdom (1988). These MOUs acknowledge mutual recognition of the adequacy of inspectional programs in the participating countries and permit the exchange of data between the countries without need for independent verification by the recipient country.

REFERENCES


4. Survey by Dr. Jean M. Taylor.


References

Contents

Copyright © 2003 Marcel Dekker, Inc. Sandy Weinberg
Muhlenberg College, Allentown, Pennsylvania, U.S.A. Gerald
J. Whartenby Muhlenberg College, Allentown, Pennsylvania,
U.S.A. Copyright © 2003 Marcel Dekker, Inc.
Chapter 1 Historical Perspective

Copyright © 2003 Marcel Dekker, Inc.
Chapter 5 Implementing GLPs in a Non-GLP Analytical Laboratory

Good Laboratory Practice Standards, 40 CFR part 160, 40 CFR part 792, 21 CFR part 58.


RELEVANT WEBSITES


EPA TSCA GLPS: www.ovpr.uga.edu/qua/tscatoc.html.

EPA GLP ADVISORIES: www.ovpr.uga.edu/qua/advisor2.html.

EQP GLP FAQ: www.ovpr.uga.edu/qua/qna.html.

EPA GALPS: www.epa.gov/docs/irm_galp.


Copyright © 2003 Marcel Dekker, Inc.
Dice B. operations manager, telephone interview, Hyattsville, MD, April 25, 1990.


Gardner E. System opens access to physicians, restricts it to others. sidebar. Mod Healthcare 38, Nov. 3, 1989.


Garwood RM. FDA’s viewpoint on inspection of computer systems.


Hubbert J. Data base concepts. EDP Aud spring 1980.


Kuong JF. Auditor involvement in system development and the need to develop effective, efficient, secure, auditable and controllable systems. keynote speech at the First Regional EDP Auditors Conference, Tel-Aviv, Israel, June 3, 1982.


Kuong JF. Organizing, managing and controlling the EDP auditing function. seminar text, Management Advisory Publications, 1980.


MALVERN. Sizing up to GMP. Soap, Perf Cosmet 69.9: 45, 1996.


Copyright © 2003 Marcel Dekker, Inc.


Copyright © 2003 Marcel Dekker, Inc.