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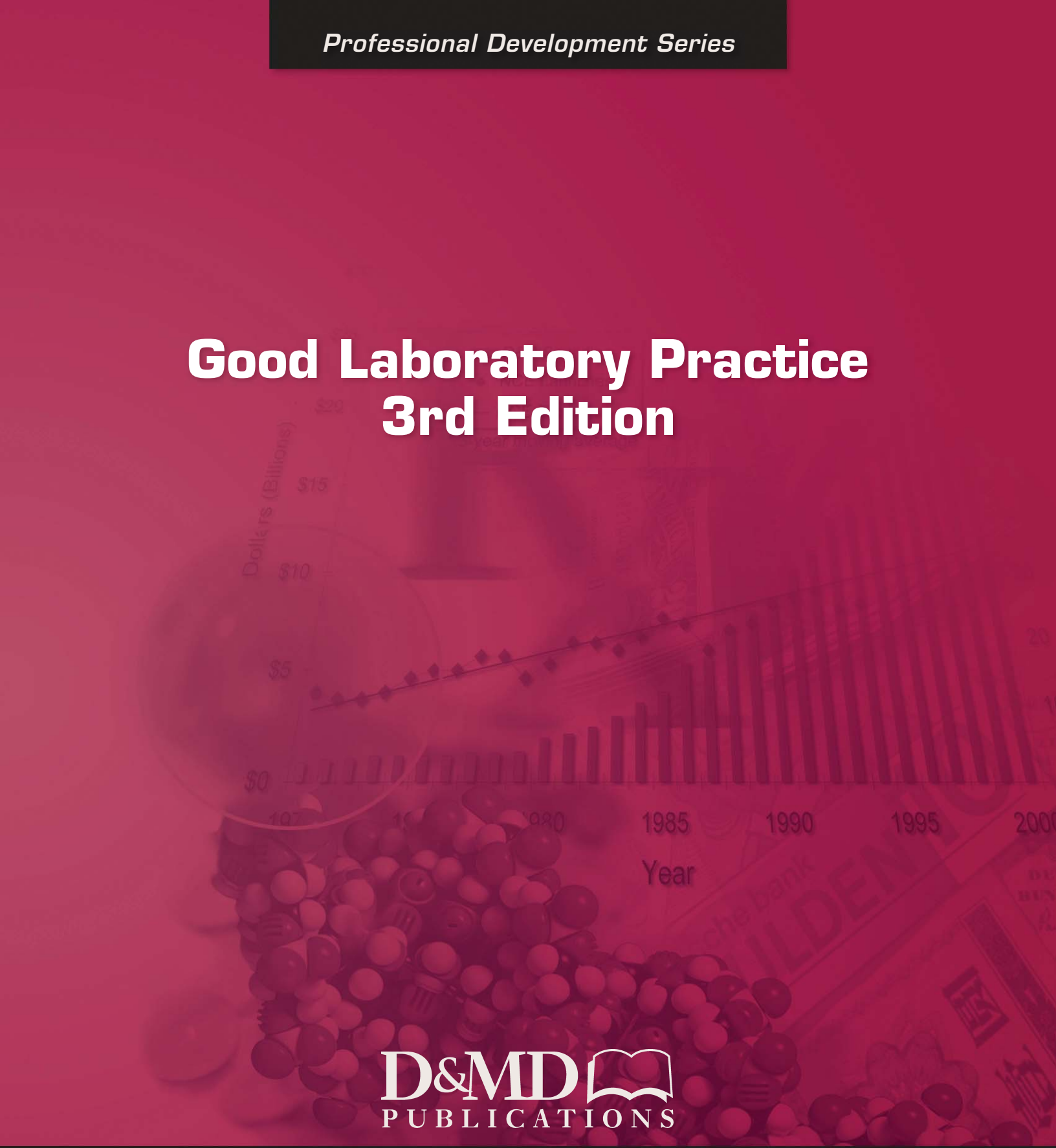
Good Laboratory Practice
3rd Edition



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By Alex D. Kanarek, Ph.D.

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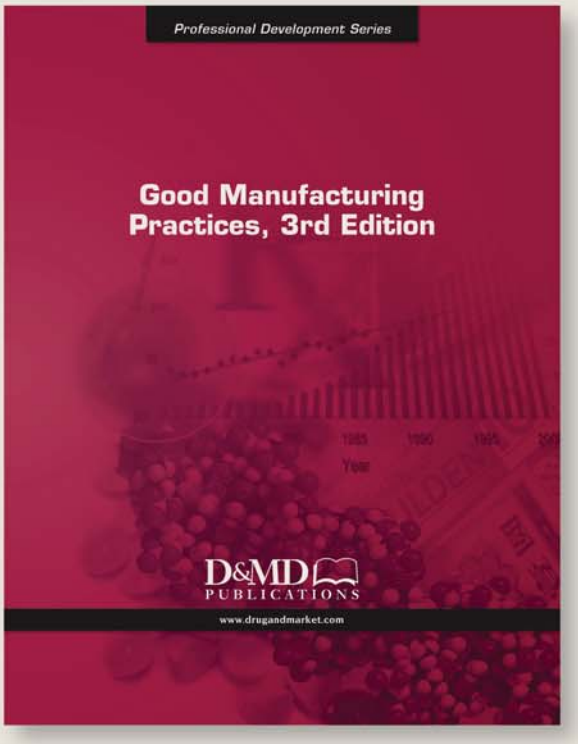

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Good Laboratory Practice

3rd Edition

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Dr. Alex Kanarek received his B.S. with Honors from Imperial College, University of London and his Ph.D. from Cambridge University. He has operated his own consultancy (originally Bio-Development Consulting Services, now AK Consulting) for the past 14 years. Based upon more than 30 years' experience in the biopharmaceutical industry with the Wellcome Foundation (now GlaxoSmithKline) in the UK and Connaught Laboratories (now Sanofi Pasteur) in North America, his consultancy has specialized in technology transfer, biopharmaceutical development and regulatory compliance in development and manufacturing laboratories. In addition to this third edition of his successful *Guide to GLP*, Dr. Kanarek has written Drug and Market Development's *Guides to Good Manufacturing Practice, Good Clinical Practice, Good Validation Practice and Good Facility Design*, as well as the first and second editions of the market analysis report, *The Bioprocessing Industry*. He was contributing editor of the monthly Bioprocess News for the first 18 months of its existence and continued to contribute to the Regulatory Notes column until it ceased publication. Dr. Kanarek is now on the Editorial Advisory Board of the BioProcess International journal.

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CHAPTER 1: EXECUTIVE SUMMARY

New drug discovery and development becomes more difficult and more expensive every year. The larger pharmaceutical companies continue to seek new leads outside of their own research laboratories in order to control R&D costs, or to extend their portfolio. This is particularly true in the biopharmaceutical area, since most traditional pharmaceutical companies have had limited direct experience in this field and prefer to license-in such technology. Alternatively, the smaller biotechnology company may be acquired by the larger partner. In the same week in May, 2007, two major US companies both published their intent to invest further in biotechnology incubator companies (Pfizer, Inc.) or the purchase of biotechnology companies with late-stage products, especially vaccines (Merck & Co.).

In all of these cases, the new product leads will be of increased value to the acquiring partner if the principles of Good Laboratory Practice (GLP) have been followed by the originating scientists. In any drug development program, but especially with the acquisition and further development of any new technology by a major industrial partner, the term "time to market" becomes all-important, since each month lost in the laboratory is a month when the product is not earning revenue to pay back the ever-increasing costs of development and testing. The drug development and testing timeline is being extended by more stringent regulatory requirements, especially in the pre-clinical testing stages. Time to market will be extended, with negative commercial impact, if critical early research work and drug testing has to be repeated under more strictly controlled conditions in order to comply with the GLP regulations.

These regulations were introduced first in the USA in 1979 and revised in 1987. They were intended to assure the quality and integrity of any pre-clinical safety or efficacy data, especially animal testing data, which would be submitted in support of an application to start testing a drug in human subjects, or for approval to market the new drug on completion of the clinical trials. The regulations cover all key areas of pre-clinical laboratory work, including facilities and operations, personnel qualification and training, study design and execution, data recording and archiving and quality assurance procedures. The same requirements may apply in those laboratories which are testing samples derived from clinical studies—in some countries, the concept of Good Clinical Laboratory Practice has been introduced, as a supplement to GLP and to Good Clinical Practice regulations.

University laboratories, spin-off companies and smaller drug development companies which therefore undertake to apply GLP to their work as soon as it is required, are those which can attract greater attention from potential industrial partners. Alternatively, if the smaller new companies prefer to proceed to further independent development before approaching "Big Pharma", they can gain a more rapid acceptance of their experimental results by the regulatory bodies, leading to earlier qualification of the drug for clinical studies. Contract laboratories

offering pre-clinical testing services will have to be able to demonstrate to their clients and the regulatory bodies that their operations are fully in GLP compliance. Companies planning to extend their work beyond the bounds of North America will benefit from a better understanding of the OECD principles of GLP and their practical application.

This Guide examines the GLP regulations of the U.S.A. and other countries in detail and gives firm guidelines for compliance, using as a basis the GLP requirements published in the U.S.A. Code of Federal Regulations, Title 21, Part 58, 2006 Edition (21CFR58). The regulations laid down by other countries, especially the members of the European Community, are based upon guidelines developed by the Organization for Economic Development (OECD) in 1980. These are very similar to 21CFR58 and have been updated regularly. Guidelines on safety testing and analytical methods issued by the International Conference on Harmonization (ICH) are also reviewed. Those rules which are most commonly cited by FDA inspectors for non-compliance are highlighted. Since compliance is finally determined by official inspections of the laboratory organization and operations, and by audits of data and reports, special attention is paid to documentation and the preparations for internal and external inspections and audits.

The recommendations presented in this Guide have been distilled from a large body of information and opinion. The most recent guidelines issued by the FDA and other regulatory authorities to industry and to their inspection staff have been accessed. Opinion and advice collected from other regulatory consultants, including ex-FDA personnel, has been reviewed. With this Guide, the task of GLP compliance is made easier to understand and to achieve.

CHAPTER 2: INTRODUCTION

The Assurance of Quality in Drug Research, Development, and Pre-Clinical Testing

The theme of this Guide is the assurance of quality in research and development and how this has been mandated by government agencies responsible for the approval of the clinical testing and marketing of new pharmaceutical and biological products. The first edition, published at the end of 1999, was intended to explain this topic to academic researchers and those who had established spin-off companies to develop university discoveries in the commercial world. At that time it appeared to me that there was a dearth of knowledge on GLP in this population and that good research was being wasted due to lack of regulatory compliance. Three years later, looking at the list of companies that had purchased copies of this Guide, it became clear that a need to be more familiar with GLP knowledge existed at nearly every level of the pharmaceutical industry. The second edition therefore broadened its approach, so as to provide better assistance to industrial researchers and those companies which are relying upon the work of contract research organizations (CRO) to perform GLP-compliant research and testing. This third edition, seeks to incorporate the most recent information available on compliance techniques and reviews in more detail topics, such as analytical method qualification and validation, which are regularly discussed when GLP specialists meet with research and development scientists and those responsible for quality assurance in GLP laboratories.

Every research scientist aims to produce work of the highest quality. They study the science and become highly qualified in the discipline. They hone their techniques and train assistants well. They plan and run their experiments with meticulous care, collect and report the data with the utmost objectivity and draw their conclusions with the rigorous application of logic and with due reference to previous work in the field. The researchers also submit published reports on these same techniques, observations and conclusions to the scrutiny of their peers, who will not hesitate to point out any shortcomings they may observe. In an industrial environment, internal reports and the review of these by project teams will fulfill the same functions.

Why, therefore, is there a need for the "assurance of quality" in this work?

Simply because, as it has been said of justice: "it must not only be done, it must be seen to be done," especially when the results of the research and development are to be applied to the prevention or treatment of disease. Then they must be reproducible and reliable to the satisfaction of the regulatory bodies established to assure the safety and efficacy of the drugs and biologicals before they are marketed for use. These bodies rely upon comprehensive documentation of the work and on its surveillance by independent persons charged with the task of assuring the quality

of the studies. They will also subject the research, the facility, and the personnel responsible to rigorous inspections before approving the next stage of the drug's development.

This assurance is designed to remove from the experimental arena those factors that may cause a lack of reproducibility in the experimental results or bias in observations. The factors can be as diverse as the unexpected contaminant in a purchased lot of chemicals or an unadvised change in a commercial animal feed. They may also involve the tendency for a particular thermostat to produce an incubator temperature one degree higher than that indicated by its control dial, the reading of that temperature one degree lower than actual by a particular thermometer placed in that incubator, and similar mechanical errors. They may certainly involve the tendency for a certain technician to jot down his or her observations on a piece of paper and then occasionally make unchecked errors in transcribing those data to the permanent laboratory record book.

Quality Assurance (QA) (see definition in Exhibit 2.1) is therefore needed to detect those factors and to guide and monitor the selection and training of the staff, their design and execution of the experiments, and the recording and interpretation of the data. The aim is to reduce the unforeseen and unplanned variables to an absolute minimum. The quality of research work, like any other product, must be designed into the work before it starts, and monitored during its performance. It cannot be created after the work is completed.

Exhibit 2.1 What is Quality Assurance?

Definitions of "Quality" 1. The Nature of Something (i.e., its Constitution or Character) 2. Excellence or Goodness or Virtue
Definitions of "Assurance" 1. Sureness (i.e., Certainty, Dependability) 2. Confidence (i.e., Security, Guarantee) 3. Verification (i.e., Certification, Validation)
"Quality Assurance" is a means of guaranteeing the excellence, security, and dependability of a process (e.g., an experiment, test, observation or report), or its product (e.g., a new drug) by monitoring, validating, and certifying the constituent parts of the process, its overall operation, and the tests applied to it.

Source: D&MD Publications.

Good Laboratory Practice and the Transfer of Technology

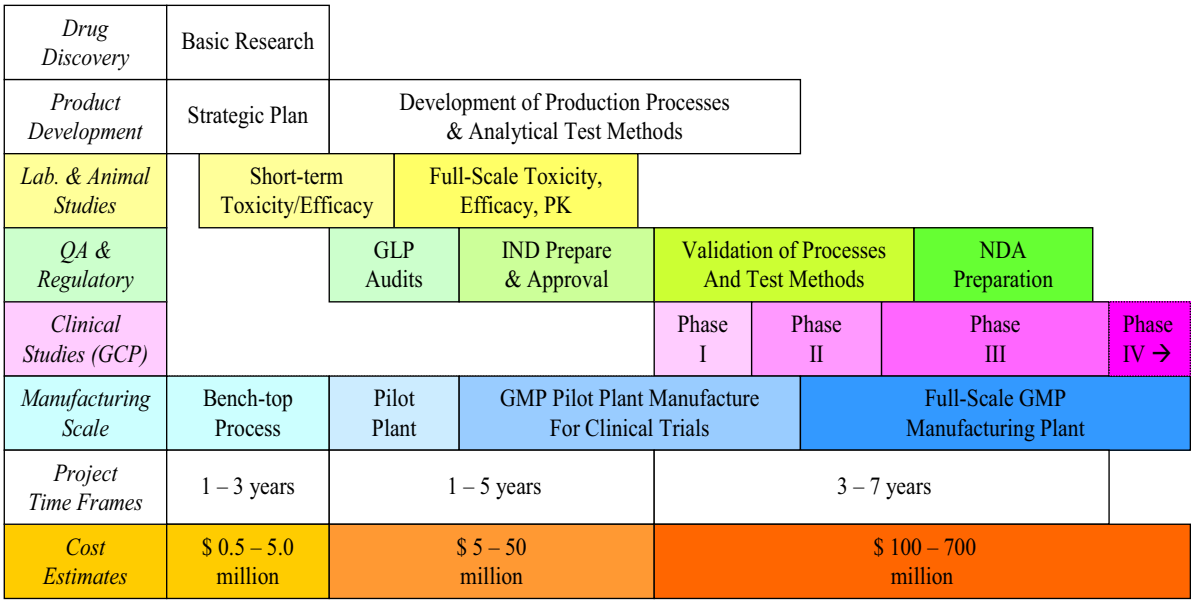
Good Laboratory Practice (GLP) has been defined by the international organization, Organization for Economic Cooperation and Development (OECD), as "a quality system concerned with the organizational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported."

The first application of GLP in drug development may arise while the research is still in the discovery laboratory or at the earliest stages of industrial development. In the current economic climate, increasingly there is a need for university pharmaceutical research to be designed for commercialization. Discoveries with any commercial potential are immediately patented and dedicated university technology transfer officers will seek to license these patents to companies seeking to exploit the research rather than performing it themselves. The licensing-in or support of independent biotechnology research by the larger pharmaceutical companies is a major example of this approach. "Big Pharma" may prefer to invest money in the endeavors of a small, specialized laboratory with some strong drug development platform and intellectual property protection rather than seek to establish a new team to do similar research in-house. But technology developed in academia, if it is to realize any commercial potential, must eventually be transferred to the industrial world and meet its criteria of quality.

This transfer may take place at various stages in the development of a particular drug candidate. These stages are illustrated in Exhibit 2.2. These days it is common for the university to sponsor the establishment of a "spin-off" company, often housed in an incubator facility, where the first steps in commercialization may take place. This small enterprise may attract development funding from a larger company in exchange for rights to the exclusive marketing of the potential product.

Following that, the typical scenario is for the larger industrial partner to become directly involved in the development process when major expenditure must be incurred or expertise is needed that is missing in the smaller partner. This will principally occur when the clinical stages are approached. The alternative, more traditional route, is for the entire process to be performed within the same company. Under these circumstances, it is to be expected that the basic research scientists will have been sensitized to the requirements for GLP compliance, but this is not always so. Up to the submission of the clinical trial application to the regulatory body, the "pre-clinical" work is concerned with the full characterization of the active principle, the demonstration of the activity and safety of the drug in animals and the development of a suitable manufacturing and formulation process that can be scaled up to industrial levels.

Exhibit 2.2 The Stages in Drug Development



Source: D&MD Publications.

In order to obtain approval to start a Phase I trial of a new product, an application, known in the USA as an "IND"—Investigational New Drug application—must be filed with the regulatory authorities. This document will contain the reports of all preclinical testing which characterized the active principle and studied its activity and safety in laboratory animals.

The studies will have produced a pharmacological and pharmacokinetic profile for the drug, including information on its mechanism of action, dose-response or concentration-response relationships, suggested routes of application and the absorption, distribution and excretion of the drug and its metabolites. These studies must be performed under GLP rules to be acceptable to the authorities. The product to be tested clinically, especially in later trials, must be manufactured under GMP conditions, preferably in a formulation which approximates closely to that which is intended to be marketed.

It is in the pre-clinical efficacy and safety testing that the formal application of QA to research and development becomes essential. As is detailed in Chapter 3, most government authorities have in place GLP regulations requiring that certain control practices are applied to these tests. In the United States, and the other countries considered in Chapter 3, the results of tests for efficacy and safety in animals cannot be included in formal submissions to the FDA or the corresponding

regulatory agencies elsewhere unless they were performed in compliance with GLP.

One reason why the larger partner will take over the development program is that it already has laboratories operating in compliance with GLP and staff familiar with these requirements. At this point, certain work already done by the university laboratory, or the incubator spin-off, which was not done under GLP compliance, may need to be repeated by the industrial laboratory, since it is critical to the clinical application. How much better would it be if the academic/spin-off partner were able to show that its critical experiments were already in compliance? The confidence that the pharmaceutical company may place in the work of the academic partner can rely heavily on the competence of the university staff to demonstrate their understanding of GLP requirements and constraints and their ability to produce work that satisfies the most critical QA inspectors.

On the other hand, if the development work is being done in an industrial laboratory, it is essential that GLP is applied to all aspects of the development process. In this case, the company must assure that new scientists and technical assistants joining the company are aware of the provisions of GLP regulations and are trained in compliance from day one. There have been instances in which senior scientists taking over responsibility for major R&D projects in a commercial setting do not respect the reasons for performing research in a certain way, especially with regard to laboratory records, and may jeopardize the company's ability to obtain approval for clinical trials based upon the work. Seniority does not excuse lack of GLP compliance. The persons concerned must be made aware that insistence on compliance with GLP procedures is not a criticism of the quality of the science, but is based on a need to show that the quality of the science has been assured by proper planning, monitoring, and validation of the experimental work. In most cases, the proper application of the guidelines for documentation and experimental conduct will suffice to satisfy these QA needs.

The transfer of processes and procedures within the company, for example, from the development suite to the pilot plant and thence to full-scale manufacturing, is made much easier when all concerned are using the same methods to perform experiments and tests, record their results, and report their findings. If the company is using an outside laboratory to perform any special toxicity or pharmacology studies, the management of the sponsoring company must be assured that the contract research laboratory can deliver results that will support the regulatory submissions. The use of good laboratory practices (and the capitals are deliberately not used) is simply the application of common sense to the work that needs to be done to bring a new drug to the market. The formalization of these practices and the harmonization of the regulations that describe them is intended to ensure that R&D results are acceptable to regulatory authorities throughout the world. This only means the drug gets to the market faster—a goal recognized by all of us as prime and critical.

The Cost of GLP Non-compliance

Specialist contract research organizations (CROs), that have become recognized experts in GLP compliance in pre-clinical studies, are a major success story in the drug development industry. This is simply because they have shown that it is more efficient use of time and money to perform a pharmacokinetic or toxicity study once properly, in full compliance with GLP, than to have your work referred back by the regulatory authorities for additional studies or repeat testing to satisfy their requirements. Many pharmaceutical companies that do not have the expertise or facilities in-house are prepared to pay the extra cost of using a CRO to assure the acceptability of the results generated, especially when very specialized tests are needed.

With the drug development pipeline lengthening continually and competitive pressures growing, a reduction in the time spent by a company bringing a new entity to the market is critical to success. Each month a new drug is awaiting approval may cost the company up to $1.0 million in lost sales, even for a product projected to take a very modest market share. "Blockbuster drugs" may have a revenue potential of $500 million to 1 billion per annum across the developed world. It is obvious that the first firm to market will also be enjoying relatively less competition.

Apart from the cost of delayed sales revenue, the cost of repeating critical studies, especially in animals, is not inconsiderable. A chronic toxicity study, involving at least two species of animal, over a period of six months to one year, with the associated histopathological work, may cost $250,000 to $500,000. Pharmacokinetic and toxicity studies in primates, which may be needed for certain specialist drugs, may be priced at $1.0 million to $1.5 million, since the cost of the animals alone, apart from their maintenance, will run to $200,000 for a relatively small group.

Since compliance with GLP will ensure that the study is properly designed, performed, and reported, the economic advantages of understanding the regulations and managing the laboratories so that the regulations may be observed are enormous. It is for this reason that this book is designed to assist those scientists and managers responsible for academic research, commercial start-up research and development operations, or established industrial laboratories to understand the impact of GLP requirements on their work and to assist them in achieving full compliance simply and inexpensively.

CHAPTER 3: INTERNATIONAL REGULATIONS GOVERNING GLP

This chapter is concerned with the actual text of GLP regulations from several different countries and the similarities and differences to be found in these texts. This study is necessary for those laboratories that plan to seek approval for their products outside of the United States and Canada, especially in Europe and Japan. The United States was the first country to formulate formal legislation for this purpose and thus other regulatory bodies have tended to use the U.S. text as a basis for their domestic documentation. The move toward harmonization of international drug regulations, strongly propagated by FDA, the Organization for Economic Cooperation and Development (OECD) and subsequently the European Union (EU) legislature, has meant that current regulations are virtually interchangeable. This chapter will examine, however, the way in which the regulations of the United States, Canada, the OECD, and Japan developed, so as to understand fully the current status.

Chronology and Current Regulations

United States of America

In the 1970s, inspections of nonclinical laboratories revealed that some studies submitted in support of the safety of regulated products had not been conducted in accord with acceptable practice. As a result, the data from such studies was not always of the quality and integrity to assure product safety. These findings led the Food and Drug Administration, responsible for the regulation of drugs, biologicals, medical devices, cosmetics, and foods, to publish "Good Laboratory Practice regulations for nonclinical laboratory studies" in the Federal Register (Ref: 41FR600 13) on December 22, 1978 and this became a Part of the Code of Federal Regulations (CFR). The document was codified as 21CFR Part 58 and became effective as of June 20, 1979. The CFR is updated every April, however, the first major revision of Section 58 was on September 4, 1987. This was the result of the Agency's experiences in administering the regulations and discussions between FDA and representatives of testing laboratories over the previous three years. The stated intention was to permit nonclinical testing laboratories greater flexibility in conducting nonclinical laboratory studies without compromising public protection. Major changes were made in the sections dealing with quality assurance, protocol preparation, test and control article characterization, and retention of specimens and samples. The preamble to the Final Rule published in 1987 gives some useful indications of the Agency's thinking on some points of interpretation of the rules and these are referenced as necessary in this text. Other minor revisions to individual Subparts of the Regulations occurred in March 1985, March 1989, July 1991, March 1994, April 1999 and March 2002. The version issued in April 2006 is used here. The U.S. Environmental Protection Agency also publishes two sets of GLP regulations for studies related to

the health, environmental, and chemical effects of toxic substances and for pesticide studies. These are basically similar to 21CFR58.

In addition, the use of computerized systems in GLP laboratories comes under the provisions of 21CFR1 1 "Electronic Records; Electronic Signatures." Such systems would include those involved in the operation of specialized equipment, such as gas chromatographic apparatus and mass spectrometers, and laboratory information management systems (LIMS) for the collection and handling of data. Part 11 was issued in March of 1997, providing criteria for acceptance by FDA of electronic records, electronic signatures, and handwritten signatures executed to electronic records as equivalent to paper records and handwritten signatures executed on paper. These regulations, which apply to all FDA program areas, were intended to permit the widest possible use of electronic technology. After Part 11 became effective in August 1997, significant discussions ensued among industry, contractors, and the Agency concerning the interpretation and implementation of the regulations. Compliance with this regulation has presented difficulties for many laboratories, especially if they are using computer systems installed before this regulation came into effect, the so-called "legacy systems." In order to assist industry, FDA issued several Guidances in subsequent years. Finally, in February 2003, the principal draft Guidances were withdrawn and industry was informed by FDA that application of the requirements of Part 11 would be restricted so as to reduce the cost of the program to industry and encourage technological advances. A new Final Guidance was issued in August 2003. It is this document which will be used in the analysis in Chapter 4.

The Organization for Economic Cooperation and Development (OECD) and the European Union (EU)

The Organization for Economic Cooperation and Development, established in 1961, is not a regulatory agency but a cooperative effort by the 24 member nations to promote economic development by coordinating national policies. The member countries of the OECD are shown in Exhibit 3.1.

Exhibit 3.1 Member Nations of OECD

Those nations that are also members of the European Union are shown in italics.

Australia	*France*	Japan	*Spain*
Austria	*Germany*	*Luxembourg*	*Sweden*
Belgium	*Greece*	*Netherlands*	Switzerland
Canada	Iceland	New Zealand	Turkey
Denmark	*Ireland (Eire)*	Norway	*United Kingdom*
Finland	*Italy*	*Portugal*	United States

Source: D&MD Publications.

Thus, in order to improve the harmonization of drug and chemical testing regulations, OECD in 1981 adopted a set of GLP "Principles" that had been developed by a series of working parties chaired by a member of the U.S. Environmental Protection Agency. The FDA regulations of 1978 formed the basis for the discussions. These Principles did not have the status of legal requirements, but members of OECD agreed to use them in national compliance programs, both for pharmaceuticals and for other environmentally important chemicals such as pesticides. The main intention was to allow the tests performed on a product in one country to be accepted by the regulatory agencies of other member countries. Systems were put in place whereby laboratories performing tests according to the Principles would be registered by the local regulatory body as "GLP compliant."

The Principles were accorded legal status by their adoption by the European Economic Community (now the European Union) Council in 1986. A Directive was issued to EU members requiring them to enact suitable legislation to ensure that laboratories testing "chemical products" would comply with the OECD "Principles of Good Laboratory Practice." The most recent EU Directives are described in § 3.1.3, below.

After further working-group meetings in 1995 and 1996, the Principles were revised in 1997 and published by the OECD as ENV/MC/CHEM(98)17 in 1998. The scope of this document includes human and animal pharmaceuticals and biologicals, pesticides, cosmetics, food/feed additives, and industrial chemicals. It is this document that is referred to in this analysis. Several Guides were also published in a "Series on Principles of GLP and Compliance Monitoring" to assist member countries in performing inspections and to detail further the responsibilities of the Study Sponsor, the Study Director, and the QA Unit. These documents are listed in Exhibit 3.2. Many of

them were revised in 1999. The universal applicability of some of these guidelines make them appropriate reading for all GLP laboratories. They can be accessed on the Internet, as detailed in Chapter 8.

Exhibit 3.2 OECD Documents Concerning GLP and Compliance Monitoring

Title	Reference
OECD Principles on Good Laboratory Practice	ENV/MC/CHEM(98) 17, 1998
Revised Guides for Compliance Monitoring Procedures for Good Laboratory Practice	OCDE/GD(95)66, 1995
Revised Guidance for the Conduct of Laboratory Inspections and Study Audits	OCDE/GD(95)67, 1995
Quality Assurance and GLP (Revised)	ENV/JM/MONO(99)20, 1999
Compliance of Laboratory Suppliers with GLP Principles (Revised)	ENV/JM/MONO(99)21, 2000
The Application of GLP Principles to Short-term Studies (Revised)	ENV/JM/MONO(99)22, 2000
The Application of GLP Principles to Field Studies (Revised)	ENV/JM/MONO(99)23, 1999
The Role and Responsibilities of the Study Director in GLP Studies (Revised)	ENV/JM/MONO(99)24, 1999
Guidance for the Preparation of GLP Inspection Reports	OCDE/GD(95)114, 1995
The Application of the Principles of GLP to Computerized Systems	OCDE/GD(95) 115, 1995
The Role & Responsibilities of the Sponsor in the Application of the Principles of GLP	ENV/MC/CHEM(98) 16, 1998
Requesting and Carrying Out Inspections and Study Audits in Another Country	ENV/JM/MONO(2000)/3 2002
The Application of GLP Principles to the Organization and Management of Multi-Site Studies	ENV/JM/MONO(2002)/9 2002
The Applications of the Principles of GLP to *In Vitro* Studies	ENV/JM/MONO(2004)26 2004

Source: D&MD Publications.

Europe

The Council of the European Union issued Directives to member states on GLP, the most recent being as follows:

Directive 2004/9/EC replaced Directive 88/320/EEC. It requires member states to designate the authorities responsible for GLP inspections in their territory. It also lays down requirements for reporting and the mutual acceptance of data. The Directive requires that the OECD Revised Guides for Compliance Monitoring for GLP and for the Conduct of Test Facility Inspections and Study Audits must be followed during laboratory inspections.

Directive 2004/10/EC replaced Directive 87/18/EEC. It requires that member states must take all measures necessary to ensure that laboratories carrying out safety studies on chemical products comply with the OECD Principles of GLP.

Canada

The Canadian Ministry of Health and Welfare, usually known as Health Canada, has a Health Protection Branch. This regulates drugs, biologicals, cosmetics, devices, foods, and other products that may affect human or animal health. It publishes the Food and Drugs Act and the Regulations derived from the Act. These are split up into individual Schedules, (identified by capital letter). Schedule C covers drugs and biologicals. Surprisingly, however, the Schedule does not contain any specific regulations for Good Laboratory Practices.

The submission, in Canada, of data to support a pre-clinical new drug submission (for approval to proceed to clinical trial of a new drug—(a CTA, equivalent to the USA's IND) is covered in Section C.05.005, in which the contents of the Investigators' Brochure are listed, including the results of pre-clinical testing. New drug submissions for approval to market a new drug (NDS = USA NDA) are covered in Section C.08.005.1, now updated to April 30, 2003. Both sections specify the reports to be included in these submissions and specifically mention reports on animal and *in vitro* studies. They do not lay down any criteria for such studies, apart from requiring the summarizing and description of experiments which generate raw data, the means of analysis of the data, and the results and conclusions of the study.

However, a submission certificate is required, which should certify that all information and material included in the submission, or supplement, is accurate and complete, and that the sectional reports and the comprehensive summary included in the submission correctly represent the information and material referred to or included in the submission. The easiest way to provide this assurance is to follow GLP principles.

Under these circumstances, Canadian sponsors were generally advised to follow the FDA GLP guidelines in order to satisfy this regulation, and to facilitate the preparation of parallel

submissions to the FDA. However, since Canada is a member of the OECD, the conduct of nonclinical studies is now recommended to follow the Principles laid down by the OECD, described above. As an example, the Standards Council of Canada, which is recognized as the Regulatory Authority for the registration of pesticides in Canada, published "Guidelines for the Recognition of GLP Compliant Test Facilities" in April 1998. This document uses OECD's Principles as the criteria for compliance.

Japan

Three different Japanese Ministries issue GLP documents; Health & Welfare, for studies to support applications to manufacture or import drugs, International Trade, for industrial chemicals and Agriculture, and Forestry & Fisheries for agricultural chemicals (pesticides). In March 1982, the Japanese Ministry of Health & Welfare (JMHW) Pharmaceutical Affairs Bureau (PAB) issued a "Notification" No. 313 entitled "Good Laboratory Practice Standards for safety studies on drugs." This document took effect on April 1, 1983. It was revised by Notification No. 870 in October 1988, when Article 15, "Administrative facilities, etc." was deleted.

A "Pharmaceutical GLP Guideline" was published by PAB in 1995, with an English version being made available by the Japan Society of Quality Assurance for the guidance of overseas manufacturers. This text still remained very close to the original 1983 document, which was firmly based upon the FDA GLP requirements. Two other Notifications, #400 of June 1984 and #526, June 1994, dealt with guidelines for inspections and confirmation of compliance of facilities, respectively.

In March 1997, JMHW issued Ordinance No. 21, entitled "GLP Standard Ordinance For Nonclinical Laboratory Studies On Safety Of Drugs." Rather than being a guideline, this document has full legal status under the Japanese Pharmaceutical Affairs Laws and is applied to acute, sub-acute, chronic, teratology, and other toxicity studies involved in the safety testing of drugs, chemicals, and biologicals. The text of this Ordinance is more general in nature than previous Notifications, using words like "appropriate" rather than detailing the exact provisions governing the operation of test facilities.

Another document, PAB Notification No. 424, which replaced Notification #313, was issued on the same date as the March 1997 Ordinance. At the same time, Notifications #400 and 526 were abolished. PAB 424 was entitled "Implementation of Ordinance on Standard of Conduct of Non-Clinical Studies of Drug Safety." This provides considerable detail to back up the general provisions of Ordinance 21 and should be read in conjunction with the former. The detailed analyses that follow refer to both documents. The above information is based on the last English version of the regulations, which was published by the Japan Society of Quality Assurance (JCQA) in 1999. No later translations are available, but the JCQA web site also carries a reference to the revised OECD Principles of GLP, so it must be assumed that Japan is using these guidelines as

well.

Comparison of the Regulations

In this section, the three major sets of GLP regulations, namely USA 21CFR58, 1999; OECD ENV/MC/CHEM/(98) 17; and Japan Ordinance 21+PAB 424, 1997 are compared, so as to clarify their similarities and differences. The former are, naturally, much greater than the latter. There are some differences in terminology between the US/Japan sets and the OECD document, but the main contrasts are to be found in the placing of responsibility for various areas of compliance and in the provisions for dealing with instances of non-compliance.

Exhibit 3.3 shows the Table of Contents of each of the GLP sets, with each section of 21CFR58 aligned with its equivalents, wherever possible, allowing for the differences in layout of the texts. Examination of this table reveals immediately some sections of 21CFR58 that have no equivalent in the other regulations.

There are also differences to be seen in the Scope of the Regulations (termed "Aim" in Japan). Each of the sets lays out the types of tests required to be compliant and the products involved. All are concerned with non-clinical laboratory studies, especially in animals and especially to determine the toxicity and/or safety of the product under test. The purpose of the testing is assumed to be in support of the approval of the product for clinical testing and eventually for marketing for general use.

As Products, all the documents mention pharmaceuticals (Japan—"drugs") for humans and animals, biologicals, and chemicals. OECD adds pesticides, food and animal feed additives, and cosmetics; The United States has all of the above-mentioned and also includes medical devices for human use and electronic products. Thus the United States has the most comprehensive coverage.

In the sections on Definitions, these again vary from country to country, but all have essentially the same meaning. The most comprehensive set of definitions is to be found the OECD Principles, and these can serve as a very useful dictionary for general GLP interpretation. Some important definitions are shown in their varying forms in Exhibit 3.4, which also shows equivalent terms where applicable.

A particular responsibility of the Sponsor is noted in CFR Section 58.10 and the Japanese Ordinance Article 4. These state that the sponsor must notify a contract testing facility that the study must be performed according to GLP provisions. In addition, Japan Article 4 requires that the sponsor must assure that the study was performed in accordance with the Ordinance.

Beyond the Scope and Definitions, each set of GLP regulations then deals with specific

management and personnel responsibilities and the factors concerned with the operation of the test facility. These topics are dealt with in detail in Chapter 4 and any variance in the different regulations will be dealt with under the appropriate heading in that chapter.

There is one area, however, where 21CFR58 stands alone. That is in the special provisions in the Regulations for the disqualification of laboratories that have submitted studies to FDA that are found to be non-compliant with GLP. Subpart K, Sections 58.200 to 58.219 cover all aspects of this procedure, which, as far as I am aware, has been applied very rarely, if at all. The disqualification provision has two functions, 1) to exclude from an IND or FDA submission any study which has been found to be non-compliant; 2) to prevent any further studies being submitted by the facility until it can demonstrate that it is operating in compliance. In most cases, the notification by the inspector of deviations from GLP compliance usually results in corrective action by the facility and the repeat of tests under question, followed by a re-submission of the IND or NDA

OECD provides for this in the "Revised Guides for Compliance Monitoring Procedures for GLP" (OCDE/GD(95)66, 1995). This document defines the actions that result from the reporting of GLP deviations during the routine inspection or study audit of a facility. These actions may vary from granting or continuing to grant recognition of compliance where the deviations are minor and rapidly corrected, right through to refusal to grant or continuing to grant recognition where serious deviations are found. The Guides state that the latter case should result in the facility being removed from the National GLP Compliance Program and the list of approved facilities. Since the Guides are intended to be reflected in national regulatory legislation, the effect is the same as 21CFR.58.

Japan's Ordinance 21 and PAB 424 do not contain any reference to the effects of non-compliance. However, the preamble to PAB 424, which describes the implementation of Ordinance 21, states that the Ordinance is intended to specify compliance conditions for non-clinical studies and operates under the general Pharmaceuticals Affairs Law of 1961 (i.e., confirming the full legislative status of the requirements). One therefore assumes that the provisions for non-compliance will be similar to those of the other authorities.

Exhibit 3.3 Comparison of Contents of GLP Regulations

USA: 21 CFR, Section 58.	OECD ENV/MC/CHEM(98)17	JAPAN Ordinance # 21, 1997
Subpart A – General Provisions § 58.1 Scope	**SECTION I INTRODUCTION** Preface 1. Scope	**Chapter 1 General Provisions** Article 1. Aim
§ 58.3 Definitions *a) Act; b) Test article; c)Control article; d) Nonclinical laboratory study; e) Application for research or marketing permit; f) Sponsor; g) Testing facility; h) Person; i) Test System; j) Specimen; k) Raw data; l) QA Unit; m) Study Director; n) Batch; o) Study initiation date; p) Study completion date.*	2. Definition of Terms *2.1 Good Laboratory Practice* *2.2 Terms Concerning the Organization of a Test Facility* *2.3 Terms concerning the Nonclinical Health and Environmental Safety Study* *2.4 Terms Concerning the Test Item*	Article 2. Definitions 1) Test Article 2) Control Article 3) Test System 4) Specimen 5) Raw Data Article 3. Conduct of Study (applicability of Ordinance to New Drug Submissions)
§ 58.10 Applicability to studies performed under grants and contracts	NO EQUIVALENT	Article 4. Responsibilities of Sponsor.
§ 58.15 Inspection of a test facility	NO EQUIVALENT; Inspections Guidance issued in 1995 (OCDE/GD(95)67)	NO EQUIVALENT
Subpart B – Organization & Personnel § 58.29 Personnel	SECTION II GOOD LABORATORY PRACTICE PRINCIPLES 1. Test Facility Organization & Personnel 1.4 *Study Personnel's Responsibilities*	Chapter 2. Personnel & Organization Article 5. Personnel
§58.3 1 Testing facility management	1.1 Test Facility Management's Responsibilities	Article 6. Management (Responsibilities)
§ 58.33 Study director	1.2 Study Director's Responsibilities 1.3 Principal Investigator's Responsibilities.	Article 7. Study Director
§ 58.35 Quality Assurance Unit	Quality Assurance Programme 2.1 General 2.2 Responsibilities of the QA Personnel	Article 8. Quality Assurance Unit

USA: 21 CFR, Section 58.	OECD ENV/MC/CHEM(98)17	JAPAN Ordinance # 21, 1997
Subpart C – Facilities § 58.41 General	Facilities 3.1 General, para. 1.	Chapter 3. Testing Facilities & Equipment Article 9: Testing Facilities
§ 58.43 Animal care facilities	3.2 Test System Facilities 3.5 Waste Disposal	Para 9.2 Provisions for animal accommodation
§ 58.45 Animal supply facilities		Para 9.2
§ 58.47 Facilities for handling test and control articles	3.3 Facilities for handling Test & Reference Items	
§ 58.49 Laboratory operation areas	3.1 General, para 2.	Para 9.3 Testing areas
§ 58.51 Specimen and data storage facilities	3.4 Archive Facilities	Para 9.4 Archives
Subpart D – Equipment § 58.61 Equipment design	4. Apparatus, Material & Reagents 4.1 *Apparatus design* *See also: Section 5.1 Physical/Chemical Test Systems*	Article 10: Equipment Para 10.1 Equipment design Para 10.2 Installation of equipment for ease of operation, inspection, maintenance, etc.
§ 58.63 Maintenance & calibration of equipment	*4.2 Inspection, cleaning, maintenance & calibration of apparatus.*	Para 10.3 Records of equipment maintenance, etc .
Subpart E – Testing Facilities Operation § 58.81 Standard operating procedures	7. Standard Operating Procedures *- All Sections*	Chapter 4: Operation of Testing Facilities Article 11 Standard operating procedures.
§ 58.83 Reagents & solutions	*4.4 Chemicals, solutions & reagents labeling*	Chapter 5: Handling of Test Articles Article 14: Reagents & solutions
§ 58.90 Animal care	*5.2 Biological Test Systems*	Chapter 4, Article 12: Animal care.
Subpart F – Test and Control Articles § 58.105 Test & control article characterization	6. Test and Reference Items *6.2 Characterization*	Chapter 5: Handling of Test Articles Article 13.1: Characterization
§ 58.107 Test and control article handling	*6.1 Receipt, Handling, Sampling & Storage*	Article 13.3: Handling
§ 58.113 Mixture of articles with carriers	*6.2.5 Use of a Vehicle for a Test Item*	Article 13.2: Mixtures

USA: 21 CFR, Section 58.	OECD ENV/MC/CHEM(98)17	JAPAN Ordinance # 21, 1997
Subpart G – Protocol for and Conduct of a Noncinical Laboratory Study § 58.120 Protocol	8. Performance of the Study 8.1 *Study Plan* 8.2 *Study Plan Content*	Chapter 6 Protocol and Conduct of Study Article 15: Protocol
§ 58.130 Conduct of a NC lab. study	*8.3 Conduct of the Study*	Article 16: Conduct of the Study.
Subparts H-I [Reserved]		
Subpart J – Records and Reports § 58.185 Reporting of nonclinical laboratory study results	9. Reporting of Study Results *9.1 General* *9.2 Content of the Final Report*	Chapter 7. Report and Storing Article 17: Final Report
§ 58.190 Storage and retrieval of records and data § 58.195 Retention of records	10. Storage & Retention of Records & Materials Retention periods are to be specified by individual authorities.	Article 18: Storing of Study-Related Materials. PAB 424 states periods of storage are as specified in Article 26 of the Pharmaceutical Affairs Law.
Subpart K – Disqualification of Testing Facilities § 58.200 Purpose	NO EQUIVALENT The Guidance on Inspections provides for the listing of non-compliant facilities by the inspecting country	NO EQUIVALENT
S 58.202 Grounds for disqualification		
§ 58.204 Notice and opportunity for hearing		
§ 58. 206 Final order		
§ 58.2 10 Actions on disqualification		
§ 58.2 13 Public disclosure of information		
§ 58.2 15 Alternative or additional actions		
§ 58.2 17 Suspension or termination of a testing facility by a sponsor		
§ 58.2 19 Reinstatement of a disqualified testing facility		

Source: D&MD Publications.

Exhibit 3.4 Definitions of Major Terms

Notes to the Table: 1) Any simile used instead of the CFR "term" is underlined. 2) The Japan regulations are available only in an uncorrected English version. Where clarification is needed, an assumed correct version is also given

"Good Laboratory Practice" :
only OECD actually defines GLP, as follows:

A quality system concerned with the organizational process and the conditions under which nonclinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported.

Term	USA	OECD	Japan
Test Article	Any food additive, color additive, drug, biological product, electronic product, medical device for human use, or any other article subject to regulation under the act...	"Test Item" means an article that is the subject of the study (further defined under "Scope"	Any drug, chemical or biological substance or any product thereof which is subject for safety assessment (sic) (i.e.: the subject of a safety assessment)
Control Article	Any food additive, color additive, biological product, electronic product, medical device for human use, or any other article other than a test article, feed or water that is administered to the test system in the course of a non-clinical laboratory study for the purpose of establishing a basis for comparison with the test article.	"Reference Item" means any article used to provide a basis for comparison with the test item.	Any drug, chemical or biological substance or any product thereof to be tested for the purpose of comparison with test article.

Term	USA	OECD	Japan
"Study"	"Nonclinical laboratory study" (NCLS) means in vivo or in vitro experiments in which test articles are studied prospectively in test systems under laboratory conditions to determine their safety. The term does not include studies utilizing human subjects or clinical studies or field trials in animals. The term does not include basic studies carried out to determine whether a test article has any potential utility or to determine physical or chemical characteristics of a test article.	"Non-clinical health and environmental safety study" (NCHESS) means an experiment or set of experiments in which a test article is examined under laboratory conditions or in the environment to obtain data on its properties and/or its safety, intended for submission to appropriate regulatory authorities.	No definition given in Ordinance 21. PAB 424 refers to "non-clinical studies on safety of drugs performed by persons seeking approval or manufacture or import..."
Sponsor	(1) A person who initiates and supports, by provision of financial or other resources, a nonclinical laboratory study; (2) A person who submits a nonclinical study to the Food and Drug Administration in support of an application for a research or marketing permit; or (3) A testing facility, if it both initiates and actually conducts the study.	An entity which commissions, supports and/or submits a non-clinical health and environment study.	A person who commissions a study. (as defined in Article 4)
Testing Facility	A person who actually conducts a NCLS i.e.: actually uses the test article in a test system. Includes any establishment... that conducts non- clinical laboratory studies and any consulting laboratory ... that conducts such studies. Testing facility encompasses only those operational units that are being or have been used to conduct nonclinical laboratory studies.	The persons, premises and operational unit(s) that are necessary for conducting the NCHESS. For multi-site studies,... the test facility comprises the site at which the Study Director is located and all individual test sites which ...can be considered to be test facilities.	No definition in Ordinance 21.

Term	USA	OECD	Japan
Test System	Any animal, plant, microorganism, or subparts thereof to which the test or control article is administered or added for study. Test system also includes appropriate groups or components of the system not treated with the test or control articles.	Any biological, chemical or physical system or a combination thereof used in a study.	Any of (sic) animal plant microorganism or composition to which test or control article is administered or added, or used as control to the test system for test article.
Specimen	Any material derived from a test system for examination or analysis	Any material derived from a test system for examination, analysis or retention.	Any of (sic) materials collected from a test system or analysis.
Raw Data	Any laboratory worksheets, records, memoranda, notes, or exact copies thereof, that are the result of original observations and activities of a nonclinical laboratory study and are necessary for the reconstruction and evaluation of the report of that study. In the event that exact transcripts of raw data have been prepared (e.g., tapes which have been transcribed verbatim, dated, and verified accurate by signature), the exact copy or exact transcript may be substituted for the original source as raw data. Raw data may include photographs, microfilm or microfiche copies, computer printouts, magnetic media, including dictated observations, and recorded data from automated instruments.	All original test facility records and documentation, or verified copies thereof, which are the result of the original observations and activities in a study. Raw data also may include, for example, photographs, microfilm or microfiche copies, computer readable media, dictated observations, recorded data from automated instruments, or any other data storage medium that has been recognized as capable of providing secure storage of information for a time period.	The observation results and records obtained in a study.
Quality Assurance Unit	Any person or organizational element, except the study director, designated by testing facility management to perform the duties relating to quality assurance of nonclinical laboratory studies.	Q.A. Programme means a defined system, including personnel, which is independent of study conduct and is designed to assure test facility management of compliance with these Principles of Good Laboratory	The Unit which assures that the studies at the testing facilities were conducted in compliance with this Ordinance. (as defined in Article 6)

Term	USA	OECD	Japan
Study Director	The individual responsible for the overall conduct of a nonclinical laboratory study.	The individual responsible for the overall conduct of the non-clinical health and environmental safety study.	Not defined in Ord. 21.
Batch	A specific quantity or lot of a test or control article that has been characterized according to Sec. 58.105(a).	A specific quantity or lot of a test item or reference item produced during a defined cycle of manufacture in such a way that it could be expected to be of a uniform character and should be designated as such.	Not defined in Ord. 21
Study Initiation Date	The date the protocol is signed by the study director.	The date the Study Director signs the study plan.	Not defined in Ord. 21
Study Completion Date	The date the final report is signed by the study director	The date the Study Director signs the final report.	Not defined in Ord. 21

Source: D&MD Publications

CHAPTER 4: CRITICAL COMPLIANCE ISSUES

This chapter examines all the sections of the GLP regulations covering the management and operation of a testing facility in order to highlight those most critical in terms of lack of compliance. Many of the criteria will be recognized by the reader as being "simply common sense," but this does not necessarily mean that they will be complied with on a daily basis. It is essential to cultivate as logical and analytical an approach to your facility organization and operating procedures as you would apply to your experimental design. Since it is the most commonly applied and the most comprehensive, the U.S. Code of Federal Regulations Title 21, Part 58, April 2006 Edition, is used as the basis for the following analysis. References to individual sections of the CFR are given as "Subpart X, § 58.yy," however, they will usually refer to all three sets of regulations under study. Where the GLP regulations of OECD and Japan differ markedly from the CFR, as previewed in Chapter 3, the exact differences are detailed at the end of each section.

Organization and Personnel (Subpart B, §§ 58.29–35)

This topic forms the first specific section of the FDA GLP Regulations, reflecting its importance. First, the efficiency of the facility depends upon good organization. The operating staff must be aware of their precise position and its responsibilities and how their work is allocated and managed. To plan and arrange the organizational structure, start by drawing an organogram, which shows the relationships between different functions and the responsibility tree. Insert the names of the responsible managers and supervisors.

> **OECD:** Requires that the individual(s) who fulfill the responsibility of "management" are identified in a written statement.

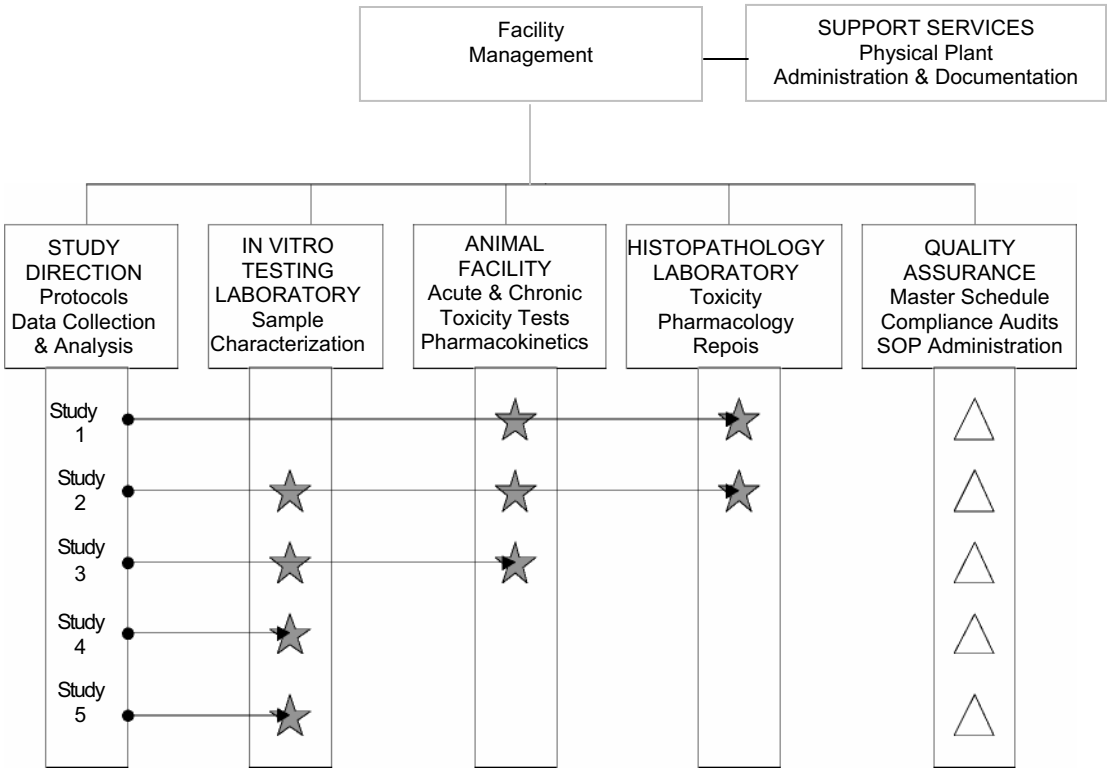
Matrix Organization

It is very likely that the best form of organizational structure for a GLP facility is the Matrix. In this format, individual functions, such as in vitro testing, animal operations, or document handling would each be run by a line manager, reporting vertically to senior management, which would also allocate appropriate resources to the function. However, the project management (i.e., "study direction") required in running a study will cut horizontally across all these functions, forming a matrix. Similarly, Quality Assurance (QA) will need to review and monitor the work of all the functional areas, so its function would also operate horizontally in the matrix. A typical matrix organogram is shown in Exhibit 4.1. In this example, Study 1 has completed in vitro testing and now has material off acute testing and under study by histopathology, while the chronic tests are ongoing. Study 2 is in all three functions, while Studies 3 and 4 have not yet completed the in

vitro testing.

Within this framework, the quality of the study will depend primarily on the quality of the people designing and running it. All three sets of Regulations studied illustrate specific requirements for the number, qualifications, and behavior of the staff and the management of the facility and describe in detail the responsibilities of the two most critical elements, the study director and the quality assurance unit.

Exhibit 4.1 Matrix Management Chart



Source: D&MD Publications.

Personnel Qualifications, Training, and Behavior (see §§ 58.29 & 58.31)

The most obvious, yet critical criterion for the personnel of the laboratory is that ***they must be qualified*** to do their job. The CFR (§58.29a) specifically require that they have the education, training, and experience to perform their assigned function. Management is obligated to provide a sufficient number of qualified staff to fulfill the work load, to keep written records of their

qualifications and job descriptions, and to assure that they fully understand their functional responsibilities (§59.29c). Implicit in this is a need to provide ***specific GLP training***, especially to new or inexperienced staff, but periodically to all staff members. This should ensure that all new or amended regulations and the facility's plans to comply with them are communicated to the entire staff, as well as providing an opportunity for the QA unit to highlight observed areas of poor compliance. GLP training is required for all levels of the personnel of a study facility. The training must be by experienced personnel, who are not only familiar with the necessities of GLP compliance, but are capable of imparting this knowledge effectively to others. Inadequate training has been highlighted as a critical source of non-compliance by GLP consultants who regularly review the findings of the FDA inspectors on behalf of the industry. Senior staff should set a good example by attending training sessions regularly.

Even the smallest laboratory must ***keep a file for each staff member***, which includes their qualifications and employment history, their current job description, a list of the studies they have worked on, with dates, and details of any specific GLP training they have received. FDA also considers that attendance at relevant scientific and technical conferences and seminars is a valuable part of a person's training and such attendances should also be listed.

Experienced staff will know that they must avoid any behavior that might result in contamination of test systems, test or control samples, or the invalidation of test results (§58.29d). There is a specific requirement for staff to wear ***appropriate, clean (or sterilized) laboratory clothing, which must be regularly changed***, for this purpose (§ 58.29e). This rule is the one most often broken by staff accustomed to working in an academic environment. Contamination control, as well as personal health precautions, also mandates that there be no eating, drinking, or smoking in the laboratories. These requirements should be dealt with by writing a simple set of "Laboratory Ground Rules" and ensuring that each staff member has acknowledged, by signature of a file copy, that they have read and understood them. A sample set of such Ground Rules is shown in Exhibit 4.2. These may be formalized as a Standard Operating Procedure document (See the Testing Facilities Operation Section of this Chapter).

Exhibit 4.2 Sample Ground Rules for Laboratory Operation

SAMPLE GROUND RULES FOR LABORATORY OPERATION

Introduction

The rules are proposed to assure the safety and efficiency of those working in The Facility. Posting these rules is not intended as an insult to the intelligence of the staff—we all forget sometimes.

That said, however, Management will consider that blatant disregard of these rules may be grounds for discipline or termination, depending upon the severity of the misdemeanor.

Protective Clothing

When in the laboratory, staff must at all times, wear clothing appropriate to the work. A full-length white coat, as supplied, is the minimum requirement. This should be worn buttoned up. Staff should also consider the suitability of footwear, from the protection point of view. Spills onto feet exposed in sandals may be dangerous. Similarly, loose, long hair may also present a hazard. Tie hair back or wear it up—it's also cooler!

Standard Operating Procedures for certain operations will lay down additional protective measures, such as hand washing, the wearing of safety glasses, gloves, masks, and/or aprons or the use of sterile clothing and accessories. These procedures must be followed rigorously. Each staff member will be issued with their own personal safety glasses. They will be responsible for keeping these available and wearing them as prescribed.

Food, Drink, etc.

No food or drink shall be brought into or consumed in the laboratories. There are vending machines and eating areas provided outside the working areas. There will be no smoking on the premises at any time.

Housekeeping

Most companies do not arrange for the cleaning of the laboratory rooms by a janitorial service. The nature and confidentiality of the work makes this unadvisable. Therefore staff members are to work in as tidy and clean a manner as possible and to clean up after themselves immediately after the work is finished.

All chemicals will be put away every night and the benches wiped down. Equipment will be cleaned as necessary, with particular attention to the control of dust and reduction of potential contamination.

Designated laboratories handling sterile or infectious materials will be washed down daily, according to the SOP, including the walls and floor, at the end of the day. The main laboratories and offices can be swept as required and the floors mopped once a week, unless spills need to be cleaned up. A special housekeeping SOP should be in place for the animal facilities. Animal staff must follow this exactly. Biohazardous waste will be placed in suitable labeled bags and autoclaved before being put out for collection.

Operation of Equipment

Operating manuals and SOPs concerning the operation of equipment and processes will be kept near the relevant equipment at all times. Ensure that you are familiar with the operating instructions, both in the manual and SOP, for any equipment before you operate it. The instructions must be followed carefully. If you are unsure about the interpretation of any instruction, ask the senior staff member present. Do not guess!

Record Keeping

In these laboratories, record keeping will have to satisfy two criteria:

a) The dating and preservation of confidential information on any new discovery or improvement to any process that might be patentable;

b) The compliance with the regulations governing Good Laboratory Practice (GLP) for non-clinical laboratories.

In the second case, only experiments and tests complying with the GLP regulations are admissible in submissions to the FDA and other regulatory bodies for clinical testing (IND) or marketing approval (NDA). Therefore, all records will be kept as follows:

- Records will be kept in the provided, labeled, numbered books, with fixed pages, which are sequentially numbered.
- All entries in these books will be in permanent ink. Any graphs or print-outs that may form part of a record must be permanently glued onto one of the permanent pages.
- A simple alpha-numeric system must be in place to identify any particular experiment or test. This number must be carried over to any pages used after the first of any entry, especially if they are not sequential.
- An experiment or test must be written up on the day that each stage is completed. Do not wait until the results are available to write up the materials and methods section.
- No entry may be erased or eliminated with "white-out" ink. Any correction to an entry must allow the original entry to be read as well and the alteration or amendment must be clearly identified.
- Each page of the book must be signed and dated by the operative and counter-signed by a senior at the end of each working day. All alterations/amendments/corrections must be similarly initialed. Glued-in records should be signed across both the original page and the glued-in section, with the date, to confirm that it is a part of the record and has not been removed or replaced.
- Before leaving the laboratory each evening, the record books in use must be returned to the office and stored in the fire-proof cabinet.

Visitors

Visitors to the laboratory will be restricted to those that have legitimate business with us. They must wear a white coat when inside the door; visitors' coats will always be available. Unless absolutely necessary for the servicing of equipment, visitors should not be allowed to handle any equipment or the company's computers.

Wherever possible, discussions with visitors should be held outside the laboratory in one of the meeting rooms available.

No casual visit by family or friends may be allowed without prior approval of the senior staff member. Children are not allowed in the laboratory for any reason. This rule is applied for their safety.

I have read and understood these rules. I agree to abide by them at all times.

Signed: _____ Date: _____

Source: D&MD Publications.

In biological testing, working with animals, microorganisms, or cell cultures, it is especially important to prevent the test system from being exposed to contaminating ***infectious agents*** which may be carried by the staff. Any person found to have an ***illness*** that may affect the outcome of a test must be excluded from the facility until the condition is corrected (§ 58.29f). Personnel are required to report to their supervisors any medical or health condition that might be considered a hazard in this respect.

Management must arrange for these people to work outside the test area, or to be laid off with pay until they may again be admitted. In small laboratories, this requirement may cause hardship due to excessive work loads or may result in delays to the testing program, and these factors may tempt the personnel to ignore the rules. However, the FDA inspectors may question staff or demand to see personnel records to confirm that these ground rules have been followed and any evidence that the study was jeopardized may invalidate the IND/NDA documentation.

OECD: Places these requirements for staff in a separate section (1.4.4), headed "Study Personnel's Responsibilities," but the rules are identical.

Japan: In the Ordinance 21, Article 5, the phrase "sanitary and health precautions" is expanded by PAB 424 to include the wearing of suitable clothing and avoidance of attendance by persons suffering from infections, etc.

Management Responsibilities (See § 58.31)

It is interesting to note that the responsibilities of the facility management are specifically described in the regulations, although one might consider that the criteria would apply to any well-managed laboratory. Nevertheless, all the authorities consider it important to assure that the management will perform certain critical tasks. ***Written documentation*** of the fulfillment of these tasks must be readily available for subsequent inspection.

Management must appoint a ***study director*** for each nonclinical laboratory study and assure that the director is replaced promptly if this becomes necessary. A deputy or acting study director may also be appointed to cover when the study director is on vacation or away for any length of time (§ 58.3 1a,b). The creation of a ***quality assurance unit*** (which may be composed of one or more people) is also specified (§ 58.3 1c). The duties of these two functions are discussed in detail later in this section.

Management is also required to provide ***adequate resources*** to perform the study, including personnel, facilities, equipment, materials (including animals), and methodology, so that the study schedule can be met (§ 58.3 1e). This again may create a concern for a small laboratory, but it is mandatory that a study is properly resourced. If there is a possibility that the resources cannot be provided in a timely manner, the study should be postponed or contracted out. FDA requires that each laboratory maintain a Master Schedule of all studies ongoing in the facility. In this schedule,

the individual studies should be indexed by test article. The study's sponsor need not be named, for reasons of commercial secrecy, but should be identified, e.g., by a code number.

Resource management is best achieved by the use of simple project management computer software, such as Symantec's "On Target" or Microsoft Project. Using these programs, the testing program can be broken down to its individual tasks. The tasks are allocated time slots and their interdependence is entered. The materials, space, and staff needed to fulfill them can be planned for by the program. The computer records can then stand as adequate evidence that management has undertaken the required resource planning in a professional manner. In the FDA's own words: ***"The master schedule sheet is the mechanism through which the QAU can assure management that the facilities are adequate and that there are sufficient numbers of qualified personnel available to accomplish the scheduled work."***

An actual example of a Study Schedule generated by "On Target" is given in Exhibit 4.3. Note that, in the example shown, for simplicity the test article is not named as required. Each major task is listed for two consecutive studies, one of which includes a pharmacodynamics investigation while the other is restricted to toxicity studies only. The GANTT chart on the right shows the interdependence of the tasks and the vertical bar chart below shows the demand for the resources of the animal unit (A.U.) that are required during these two studies. Peak demand occurs in August/September and again in October/November and the demand stays high through to the end of February 2000. Similar histograms can be generated for any other resource listed in the column headed "Resp" for "Unit Responsible," or for the expenditure that will be incurred in any given period.

The program allows the allocation of a specific number of units, be they rooms, staff, or specialized equipment, to each function and will then demonstrate the need for resource leveling by rescheduling certain study sections when demand exceeds supply. Using the same format, each of the major tasks can be further broken down.

For example, the animal studies involve the following sequential stages:

- Acquisition and quarantine of the necessary animals;
- Decontamination and cleaning of the designated testing room, with suitable caging;
- Transfer of animals to the test room and appropriate labeling;
- Preparation and administration of the test and control samples;
- Daily observation of the animals during the test period; and
- Autopsy and the taking of histopathology samples at the end of the study.

Different staff and facilities will be involved in these sub-tasks and the computer program can ensure that they will be available when the schedule requires.

Exhibit 4.3 Section of a Study Schedule GANTT Chart ("On Target" Software)

(Costs in $K)

Task Name	Duration	Start	End	Resp	Cost
STUDY # 1: Summary	217.0 d	01/Jul/99	05/May/00		$222.00
Complete Protocol	15.0 d	01/Jul/99	21/Jul/99	S.D.	$2.00
Sample Characterization	23.0 d	22/Jul/99	23/Aug/99	In.Vit	$5.00
Pharmacodynamics	10.0 d	24/Aug/99	07/Sep/99	A.U.	$20.00
Pharm. Histopath.	20.0 d	08/Sep/99	05/Oct/99	Path	$10.00
Acute Toxicity	21.0 d	24/Aug/99	22/Sep/99	A.U.	$15.00
Acute Tox. Path.	30.0 d	23/Sep/99	03/Nov/99	Path	$30.00
Chronic Toxicity	127.0 d	24/Aug/99	23/Feb/00	A.U.	$100.00
Chronic Tox. Path.	30.0 d	24/Feb/00	05/Apr/00	Path	$30.00
Write Reports	22.0 d	06/Apr/00	05/May/00	S.D.	$10.00
Report Submitted	0.0 d	05/May/00	05/May/00	Q.A.	$0.00
STUDY # 2: Summary	217.0 d	01/Sep/99	10/Jul/00		$192.00
Complete Protocol	15.0 d	01/Sep/99	22/Sep/99	S.D.	$2.00
Sample Characterization	23.0 d	23/Sep/99	25/Oct/99	In.Vit	$5.00
Acute Toxicity	21.0 d	26/Oct/99	24/Nov/99	A.U.	$15.00
Acute Tox. Path.	30.0 d	26/Nov/99	06/Jan/00	Path	$30.00
Chronic Toxicity	127.0 d	26/Oct/99	25/Apr/00	A.U.	$100.00
Chronic Tox. Path.	30.0 d	26/Apr/00	07/Jun/00	Path	$30.00
Write Reports	22.0 d	08/Jun/00	10/Jul/00	S.D.	$10.00
Report Submitted	0.0 d	10/Jul/00	10/Jul/00	Q.A.	$0.00

Source: D&MD Publications.

It has already been mentioned that management must assure that the staff understand their functional responsibilities. There is also a requirement for the documentation and rapid correction of any **deviations from the GLP regulations** during the course of a study which may be reported by the quality assurance unit (§ 58.3 1g).

This is best dealt with by a series of Standard Operating Procedure (SOP) documents that list the means whereby QA will inspect or audit operations and how reports are to be generated and handled. Advice on the writing of these SOPs and others is given in the "Facilities" section of this chapter, which deals with the operation of the facility.

Finally, there is a regulation (§ 58.31d) that often comes as a complete surprise to the management of a testing facility. This is the requirement that management must ensure that ***the samples to be tested in the study have been properly characterized*** and are fully representative of a particular stage in the development or manufacture of the drug or biological under study. Tests are required for identity, strength, purity, stability, and uniformity, as appropriate. In a later section of the CFR (§ 58.105) it is stated that the tests may be performed by the GLP laboratory or by the sponsor of

the study. One would normally expect that the responsibility for the submission of truly representative samples for testing would rest with the sponsoring development or manufacturing laboratory, but FDA places the task of ensuring that the samples tested are fully representative in the hands of the GLP facility, thus removing any gray area in the chain of responsibility. One warning letter to this effect was issued to a contract testing laboratory, after the laboratory director had stated that they were not responsible for tests performed by the sponsor. In new, spin-off facilities, where research and development and the generation of test samples may be done by associated university laboratories, compliance with this requirement may present a problem unless the characterization of the samples can be performed in the GLP test facility as well.

Regardless of which laboratory will perform the characterization testing, it will be a matter of assuring that correct test procedures are written up and followed. The samples for regulatory safety or toxicity testing should be submitted to the facility accompanied by a written Certificate of Analysis, detailing the results of the agreed characterization test program. A useful format for a ***Certificate of Analysis*** is shown in Exhibit 4.4. FDA considers that any test performed to determine the chemical nature of the test article or to determine the homogeneity and concentration of test article mixtures must comply with GLP. OECD states that each test item should be appropriately identified and the batch number, purity, composition, concentration, "or other characteristics to appropriately define each batch... should be known."

Exhibit 4.4 Certificate of Analysis

RECORD OF ANALYSIS OF SAMPLE SUBMITTED FOR STUDY # MP/321/1				
Originating Lab. Sample ID: MP/44/6		**Facility ID:**	MP/32 1/1/5	
Date Submitted: 7/23/99		**Submitted By:** B. Freumen		
Description/Active Principle/Manufacturing Stage: Extract from High-saline Run # 44 Polysaccharide fraction, Sephadex™ G-100, Cut 6.				
Tests Requested:	Antineoplastic activity, S-1 80 in mice, (to SOP AU 31-1)			
	Acute toxicity, 30-d. (to SOP AU34-2)			
SAMPLE CHARACTERIZATION:				
I.D. and Volume of Batch sampled:	High Saline Run, Lot HS44, 35 liters			
No. & Volume of Samples:	Total Volume, Cut #6 = 130 ml, Samples 10 x 2 ml,			
Sampling method:	By sterile pipette from pooled cut, under LF Hood			
Tested for:	**Identity:**	Polysaccharide	**Homogeneity:**	Single Peak
Purity: N/A	**Concentration:**	35 µg/ml	**Activity**:	TBD
	Sterility: PASSED		**Stability:**	30 Days/4°C
Sample Released By:	M. N. Roadlands	**Date:**	7/30/99	
Additional Documentation/Notes: Run description attached; Studies on purity of the single peak cut 6 are in progress. Later samples are to be better characterized.				
MNR:				
Sample/Cert. Received By:	Hugh Gothic	**Date**:	7/30/99	

Source: D&MD Publications.

The major effect of this section of the regulations would be to extend the GLP requirements beyond those studies specifically involved in safety/toxicity into the other areas of product characterization and testing. In fact, this is not necessarily a bad thing, since it will always be of advantage to show the regulatory authorities that the stricter GLP criteria were applied to any

tests on the proposed product, even at the in vitro testing stage. If both in vitro and in vivo testing will be performed in the same facility, it makes sense to apply only one set of criteria to the performance of all the tests.

In this context, it is probably a good idea to spend a few moments considering the question of analytical method "qualification" and "validation". The general regulatory attitude towards critical analytical methods, especially those applied to confirming that a batch of final drug product complies exactly with the specifications laid down for its purity and potency, is that the method must be "suitable for its intended purpose" (ICH). Simply stated, this means that a test for purity should be sensitive enough to detect very low levels of contaminants, a test for potency should be accurate and have a linear dose-response, etc. The process of demonstrating that a particular analytical method is suitable for its intended purpose is termed "Validation". Validation involves performing the test under controlled conditions, with a reliable standard preparation, in order to identify those test factors which may affect critical parameters such as sensitivity, accuracy, precision, etc. Validation runs are performed with different sets of reagents, by different analysts, until sufficient data have been collected to permit statistical analysis of the intrinsic variables in the test. Once it has been shown that these variables are controlled within a specified range, e.g. the potency of the standard is assayed at +/- 15% of the true value, then a validation report can be added to the drug development documentation.

Analytical methods used to release final approved drug product for distribution must be validated. Usually, the regulatory authorities will expect that critical tests used to characterize investigational drugs in Phase III clinical trials should also be validated, or at least be operated under a validation protocol, so that the data collected can eventually be analyzed. There is then, however, the question of what to do about those tests which are being used in the GLP laboratory, in much earlier stages of the drug development cycle. This is where the concept of "method qualification" comes in. Qualification is a term usually applied to the demonstration that process or analytical equipment is suitable for its intended purpose, so that it will yield product of reproducible quality or reproducible test results. Qualification of test methods is a newer concept which basically states that, until it is possible to perform the full range of testing required to validate a method fully, at least you can apply some controls to your method and try to show that is has some level of reproducibility, accuracy, sensitivity, etc. Using qualified methods is permissible in earlier-stage drug development. Often, the method is refined along with the improvements in the drug's purity and potency.

However, there are certain types of tests which should be validated much earlier in the drug development program. These can be defined by performing a quality risk assessment on the product and its production processes. This analysis would indicate that validation would be needed, for example, of preclinical tests in animals and man for product safety and toxicity, and laboratory bioanalyses of critical factors like blood levels of the product and its metabolites, or antibody, or other surrogate marker levels in blood or tissues. Tests to demonstrate the absence of

contaminating micro-organisms, or to validate virus removal or inactivation processes, in the case of products made in animal cell cultures, are also considered to be critical.

In addition, it is essential that data developed during test qualification studies are capable of being applied to eventual validation studies. They must be "real-world" assays, applied to processes and procedures which are going to be incorporated into the production of the final approved product. Or, it could be that the qualification work will indicate that the method is not "suitable" – and that's another valuable result.

If you are going to apply the qualification concept to GLP analytical methods, there must be a set of rules established for the control and use of test qualification. The most important will define which procedure is to be used in a particular case, according to the guidelines I have discussed. Apart from ensuring that the test method is clearly described in an SOP, it must be subject to the same change control rules as a validated test, and most importantly, the SOP should specify exactly when the qualified method can be used. Since there will be only limited experience of the test's performance, it is probably a good idea to have it performed by a more experienced analyst, who may be capable of identifying potential risks in the procedure and would know what to do to ensure that the test's variability is kept to a minimum. The proper calibration of apparatus and standards should be routine in a qualified test. Validated tests will have been shown to be more robust and able to cope better with factors that may cause variability. The trending of results should yield valuable information regarding test performance and, if validation is eventually to be done, will act as a guide to worst-case settings and acceptable specifications.

OECD: Adds to the responsibilities of management the following tasks, some of which are directly attributed to the Quality Assurance Unit in CFR:

- Appointment of one or more Principal Investigators as needed, reporting to the Study Director, to control delegated activities in multi-site studies.
- Provisions to be made for clear lines of communication between the multiple sites.
- Document approval of the Study Plan (Protocol) by the Study Director.
- Ensure that the Study Plan is made available by the Study Director to the QA Unit.
- The designation of an Archives Manager (see Records and Reports Section).
- Ensure the maintenance of the Master Schedule (see QA Unit Section).
- Establish procedures to ensure that computerized systems are suitable for their intended purpose and are validated, operated, and maintained in accordance with the GLP Principles. (In the United States, these requirements are codified in 21CFR1 1).

OECD also recommends in the Guideline "Compliance of Laboratory Suppliers with GLP Principles" (ENV/JM/MONO(99)21, 2000) that management should ensure that chemicals, reagents, animals, and equipment supplied to the facility are from suppliers that can demonstrate

that their products will enable the user to comply with GLP. The establishment of national supplier accreditation schemes is recommended. Suppliers should also implement the International Standards Organization (ISO) Standard 9001 of 1987. These proposals are dealt with in more detail later in this chapter.

Specific Appointments: The Study Director (see § 58.33)

This person is considered to be the single, fixed point of reference for the entire study. The Study Director (SD) must be professionally qualified and have adequate training and experience to be capable of taking full responsibility for the technical conduct of the study and the collection, analysis, and reporting of the test data. Mere "coordination" of these actions within the study by the SD is not considered adequate by the Agency. Note that the SD cannot be the CEO or the most senior manager of the facility, since the QA Unit must report directly to senior facility management and not to the SD. FDA has refused to allow responsibility for a study to be assigned to more than one person, as it considers that a potential would then exist for the issuing of conflicting instructions and for improper protocol implementation.

Specific responsibilities of the SD include:

- Compliance with the approved study protocol. The director will be involved in the creation of the protocol, but must assure that any changes following original approval are properly approved and documented.
- Accurate recording and verification of study data. This will be done according to a written Standard Operating Procedure. All laboratory records must be written up as the tests are read, on proper serially numbered record forms or in notebooks. The SD or an authorized designate must countersign each page of these records as being correct. If the data are then transferred to other forms or to electronic media, the SD must again assure that the final form of record complies with the original record of the findings or "raw data."
- The management of circumstances which may affect the quality and integrity of the study. All personnel must inform the SD immediately of any circumstance that may affect the outcome of the study (e.g., the failure of an air-conditioning plant in an animal room or a change in feed composition). For example, in the days before scientifically formulated animal diets, it was essential that guinea pigs being used in vaccine potency tests be fed adequate amounts of fresh greens. Absence of sufficient Vitamin C, usually supplied by the cabbage in their diet, resulted in the inability of the animals to give an adequate antibody response to the test vaccine, which then "failed potency test." Additives to today's diets may affect the outcome of a test in unexpected ways. The SD is responsible for documenting any change in test conditions and making whatever corrections may be needed.
- The use of test systems specified by the protocol. Each system, whether one in a series of in

vitro tests or a certain type of test in an animal species, will be run according to one or more SOPs. Compliance with these is ultimately the SD's responsibility.

- Compliance with all other applicable GLP regulations. As is described later, the QA unit will monitor compliance, but the SD is responsible for this study.
- Proper archiving of study raw data, specimens, and reports. It must be possible for the original data and histology specimens to be readily accessed in case of any question about the outcome of the study. The regulations specify the length of time that archived records and materials must be retained after completion of the study (see Records and Reports Section). It is the SD's responsibility to set up the archiving system for this study, which will then be maintained by designated staff.

OECD: Adds the following responsibilities for the Study Director:

a) Approval of Study Plan;

b) Ensuring that the QA personnel have a copy of the Study Plan;

c) Ensuring that the Study Plan and relevant SOPs are available to study staff (see QA Unit section of this chapter); and

d) Ensuring that computerized systems have been validated.

The eventual inspection by FDA of the conduct of the study and its results will involve the SD above all other staff. He or she must be capable of answering any questions about the study and to justify the conclusions made on the basis of the study results. This necessitates complete familiarity with the study in all its stages. The SD cannot be a remote figure in the facility, but must be prepared for "hands-on" direction and control of the study. Science and technology are so complicated and specialized today that it is almost impossible to have a study directed by even an experienced project manager if he or she has little or no direct knowledge of the processes involved. The facility management must therefore try to make managers of scientists rather than the other way round.

Ideally, a good Study Director must possess certain specific attributes to build confidence in his or her operations and findings. These are:

- Adequate post-graduate training and experience, with Ph.D., M.D., or D.V.M. qualifications and at least five years of laboratory experience in test or procedures development and operation, with an emphasis on working under criteria that are more stringent than those usually required by basic research. This type of experience is more easily gained in industry and should lead to a thorough understanding of the reasons for the study and the properties of the drug under test.
- Good managerial and inter-personal skills—the Director will need to control the progress of the study through several different functional stages, where each function may be

managed by staff with line responsibility to someone else. Good project management in a matrix organization depends on the negotiation of an agreement to perform tasks, rather than placing orders to do so, and needs understanding of the conflicts that may arise with respect to priorities and the allocation of scarce resources. The study may be compromised by the lack of interpersonal skills on the part of the SD.

- The ability to make rapid, clear, and rational decisions in the face of problems arising within the study, and to justify these decisions during the eventual QA and FDA reviews of the study.
- The possession of a methodical way of thinking that leads to the maintenance of good, clear records and dependable conclusions.

Thus the type of person needed may be found running a laboratory in industry or in charge of a pathology section in a hospital, or in a senior position in academe, but their ability to meet the criteria mentioned above has as much to do with personality as with qualifications. The skills can be sharpened by the experience of running studies, but the talent is likely inborn.

The Quality Assurance Unit (see § 58.35)

The Quality Assurance (QA) Unit, comprising one or more persons, is responsible directly to senior management for ***monitoring the compliance*** of any study with the applicable GLP regulations. The Unit must be entirely separate from and independent of the personnel engaged in the direction and conduct of that study, although the FDA does not require that a separate, permanently staffed, QA entity be established. This means that, in smaller facilities, suitably qualified personnel may be involved in one study but can perform a QA function is another study of which they are independent. QA has the authority and obligation to examine all aspects of the study regularly during its conduct and to report immediately any discrepancies found and the corrective action taken. FDA intends that "QA personnel should be able to act candidly, without bias or a real or perceived conflict of interest". QA performs its tasks by the following means:

- Maintenance of a ***master schedule*** of all ongoing studies, usually in collaboration with the project manager if there is one, or by use of the project management software. The master schedule is indexed by the identity of the test article and must describe the nature of each study, the test systems involved, the dates of the study, the SD responsible and the outside sponsor, if any. In order to preserve confidentiality, the sponsor's name may be coded, but the code must be available to FDA inspectors for reference. The schedule should indicate the current status of the study. The master schedule information is considered "raw data" within the meaning of the GLP regulations and copies of each update of the schedule are required to be maintained in the study archives.
- Holding copies of the ***protocols*** for all studies performed in the facility. There is definitely an advantage in having the QA unit involved in the actual creation of the protocol, for ease

of monitoring later.

- Performing ***regular inspections*** (sometimes called "internal audits") of each study for compliance and integrity and maintaining full records of all inspections. The record should identify the study and the phase that was inspected. As previously mentioned, any problems identified during such inspections that might affect the integrity of the study are to be reported immediately to the SD and the facility management. The record should describe any action taken to resolve these problems and any date set for a re-inspection. A full set of Inspection Forms suitable for use in internal audits will be found in Chapter 9 of this Guide. Normally, the QA unit would not need to use the entire set of forms for every study, as this includes questionnaires covering the compliance of personnel and the facility's fabric and systems. In-study inspections would mostly be confined to confirming compliance with the requirements for operation of the facility and equipment in line with the study protocol, the handling of samples, performance of tests and the generation and storage of records.
- Submitting periodic ***status reports*** on all studies to management, noting any problems and corrective action.
- Assuring that ***no deviations*** are made from approved protocols and SOPs without proper authorization and documentation. The QA unit is usually responsible for creating and maintaining an up-to-date SOP manual, and for operating the system whereby modifications to SOPs may be initiated, reviewed, and approved. The FDA does not intend that the QAU should be responsible for authorizing any deviations from the protocol or SOPs; rather it is responsible for detecting such deviations by its inspection and auditing procedures.
- QA is then also responsible for ensuring that each operating section has available in the laboratory for immediate reference the current SOPs covering its operations. FDA inspectors will look for these to be in place. A layout for the contents page of the SOP Master File or Manual is shown in Exhibit 4.5.
- Reviewing the final study report to assure it correctly describes the methods and SOPs used and that the conclusions are drawn correctly from the raw data. The QA unit is not expected to perform a scientific evaluation of the scientific procedures that were used, only to ensure that the results reported and the conclusions drawn accurately reflect the raw data. In case of uncertainties regarding test result interpretation, QA will request a meeting of senior staff to review the data and work with the SD on its interpretation. Included in the final report will be a signed statement from QA specifying the inspections performed on the study and the monitoring reports that were made.

Since the QA unit's activities described above are critical to the acceptance of the study's findings by the FDA, the regulations require that all QA procedures for inspections, reporting, and

indexing of records are maintained as written SOPs and all records of study monitoring are maintained as part of the overall study archiving.

OECD: Requires the creation of a ***Quality Assurance Program***, which covers all the above rules. The QA personnel are required to be familiar with the test procedures but not involved in the conduct of the study.

Inspections are designated as three different types: a) Study-based, b) Facility-based, c) Process-based, and these are defined by QA SOPs. The final report states which type of inspection was performed on each occasion.

Exhibit 4.5 Suggested Layout for the Master SOP Manual

SOP Number	Dept.	Original Date	Written By	Subject	Date Mod.	By	Code	Date Mod.	By	Code
M02/1-0	Man	6/5/02	DFC	Maintaining Personnel Files						
M02/2-0	Man	6/12/02	DFC	Appointment of Critical Staff	7/1/02	DFC	/2-1			
E02/1-0	Equ.	5/16/02	REG	Standardization of pH Meter						
Q02/1-0	QA	6/15/02	MNR	Writing & Maintenance of SOPs	9/1/02	MNR	/1-1	8/3/03	MNR	/1-2
Q02/2-0	QA	7/1/02	MNR	Study Inspections & Reports						
F02/1-0	FM	6/15/02	NBG	Facility Cleaning Schedules						
L02/1-0	In.Vit.	4/19/02	AZK	Molecular Weight Determination: SDS-PAGE	8/1/02	AZK	/1-1			
L02/2-0	In Vit	4/23/02	AZK	Sample Homogeneity Test:						
AU1/1-0	A.U.	5/21/02	VBP	Receipt and Quarantine of Test Animals	7/1/03	VBP	/1-2			

Source: D&MD Publications.

Exhibit 4.6 shows a typical format for reporting to management the study monitoring performed by QA in a one-month period, with some typical findings and responses. More detailed report forms are used for each individual study, covering the entire study period.

The QA records of inspection dates, the study inspected, the phase or segment of the study inspected, and the name of the individual performing the inspection must be available for FDA inspection, along with management certification that the correct monitoring procedures were followed for all reported studies. The detailed reports of audits and inspections, along with the corrective action performed are not normally accessible by FDA personnel. The intention is that the QAU should not in any way be inhibited from making a full report. In all cases, the QA function must be shown to be completely independent of study management—the SD cannot be his or her own auditor.

The importance of correct QA monitoring of the studies and the facility's operations cannot be overemphasized. Management must provide sufficient well-trained and experienced staff to fulfill all the tasks listed above. A survey published by the U.S. Pharmaceutical Research & Manufacturer's Association showed that from 1980 to 1997 the number of employees in production and QC/QA dropped by 11.7%, while staff involved in R&D and marketing almost doubled. A reduction in production staff could be explained by the use of more automation and manufacturing facility consolidation, but the loss of, especially, QA staff might explain why, in the same period, the number of warning letters issued by FDA pinpointing GLP and GMP (Good Manufacturing Practices) violations markedly increased. Although more recent QA staffing figures do not seem to be available, PhRMA has stated that the amount spent on R&D in 2002 was $32 billion, up from $1.3 billion in 1997—a very significant increase. One might speculate whether a comparative investment has been made in the QA resources.

If the facility does not have the expertise in-house to perform these critical tasks, an outside consultant should be brought in. There are many good companies now specializing in providing this service to laboratories—some are listed in Chapter 8—and they will also assist in GLP training of the facility staff, if needed. Use of an outside consultant to perform the study audits will also guarantee the complete independence of the QA reports.

Exhibit 4.6 Study Monitoring Record

QUALITY ASSURANCE UNIT

SUMMARY RECORD OF STUDY MONITORING

Period of Record: 7/1/01 – 7/31/01

Prepared By: MNR

Study Number	Monitoring Stage	Date of Audit	By	Notes/Action Taken/Approvals
MP22/3	Records	7/2/0 1	MNR	All records correctly entered; Study can proceed to final report.
MR33/2	Histopath	7/15/01	HGH	Possible confusion of specimens from animal group 2 - See Audit Report AR33/2/2, dated 7/16/01. Reserve specimens accessed for comparison slide preparation. Further report to be made following slide examination.
MZ44/43	In Vitro	7/20/01	MNR	Labeling of samples received validated, all tests complied with SOP; Test samples correctly characterized. Proceed to animal tests.
MR33/2	Histopath	7/30/0 1	HGH	Examination of reserve specimens from Group 2 confirmed identity of originals... test not compromised – OK to proceed to complete histopath. – results on both slide sets to be reported.
MC/34/4	Final Report	7/31/01	MNR	Final Report complies exactly with raw data and conclusions are correctly drawn. Report may be submitted to Sponsor. QA Report will be forwarded on 8/3/01.

Source: D&MD Publications.

Facilities (Subpart C, §§ 58.41 – 51)

This section of the GLP regulations deals with the physical plant of the laboratory, its design and construction, with special emphasis on the animal care facilities. Good research needs a reasonable

working environment, but beyond that the regulatory authorities want assurance that the study operations can be properly performed in the laboratories allocated and the results therefore will not be compromised by crowding, cross-contamination, or inadequate animal handling.

The major critical points in compliance are shown in Exhibit 4.7. Compliance is assured in this section by careful design of the facility to ensure adequate space and separation of various functions and activities. The primary aim is to avoid contamination or mix-up of samples or tests and confusion in observation and results. Note, for example, that there must be a separate area for the receipt, storage, and distribution of samples to be tested

Containment Issues

Some tests, either in vitro or in vivo, may involve handling live micro-organisms, some of which may be pathogenic to humans. In addition, certain test samples may contain toxic chemicals. For the latter, the protection of the staff and the environment can be achieved by suitable air handling, filtration, and so on, and the use of protective clothing. For the former, rules have been drawn up by organizations, such as the Centers for Disease Control in Atlanta, Georgia, for the containment of pathogenic organisms, with increasingly stringent precautions as the level of risk increases. References to the containment standards required for various types of pathogen are given in Chapter 8. In brief, the principle of "nothing in—nothing out" must apply. All laboratories should be provided with suitable chemical fume hoods and biohazard isolation cabinets.

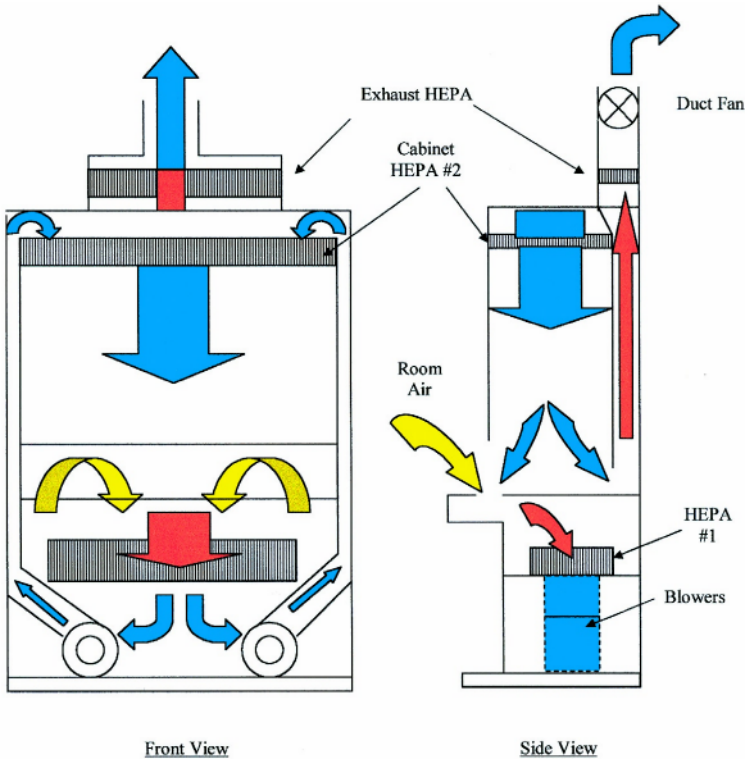
Exhibit 4.7 Critical Factors in Facility Compliance

- (§ 58.53) The facility should have animal rooms of sufficient number & size to enable: > Proper separation of animal species or test systems and studies;
    - Isolation of individual projects where necessary, especially those involving infectious or hazardous agents;
    - Quarantine of animals as needed; and
    - Specialized housing where required.
- Separate areas may be needed to isolate diseased animals for diagnosis & treatment.
- Proper waste collection, disinfection and disposal facilities are essential; they should be operated so as to minimize vermin infestation and environmental contamination.
- Other parts of the facility should be designed and designated for:
    - Handling and storage of samples, separate from the operating areas (§ 54.47).
    - Specimen and data storage (archiving), with access limited to authorized personnel (§ 58.51).
- **SOPs** must be written for the cleaning and maintenance of all areas of the facility structure. The detergents and disinfectants to be used should be from accredited suppliers and the active ingredients identified and recorded.

Source: D&MD Publications.

The prevention of contamination of bacterial or cell cultures can be achieved by the use of laminar-air-flow hoods, preferably of the Class II, B 1 type, since these also provide a measure of biohazard containment (Exhibit 4.8). The exhaust may be ducted to outside under critical conditions.

Exhibit 4.8 Biohazard Laminar-Flow Cabinet, Class II Type B1



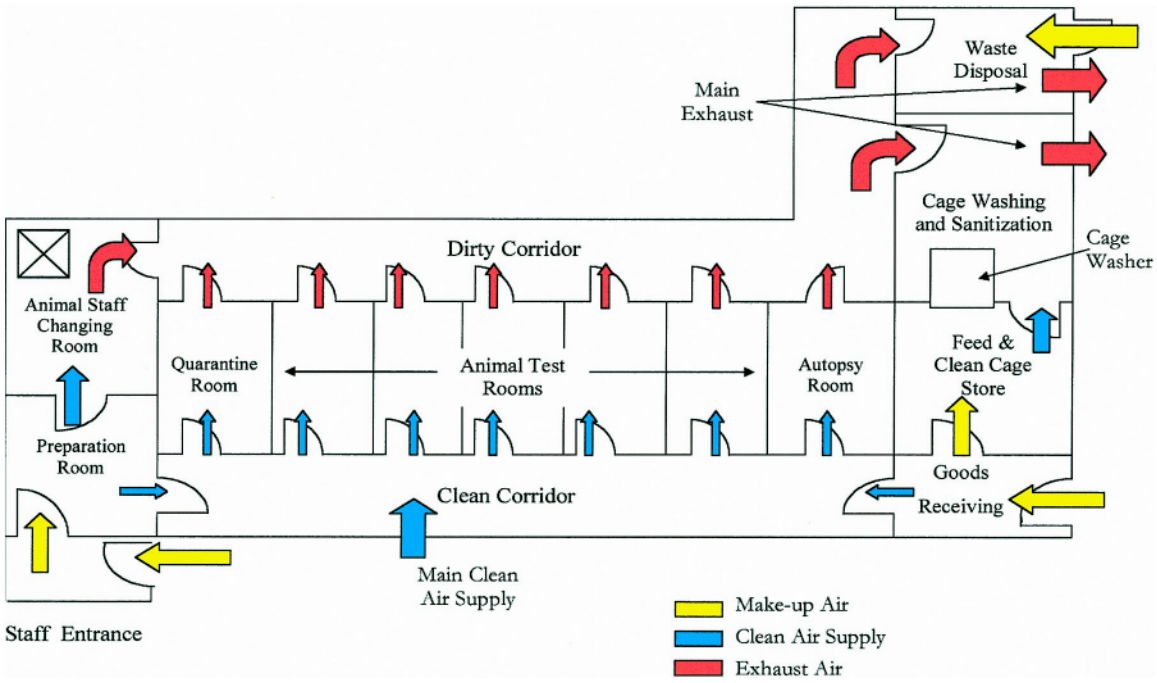
Source: D&MD Publications.

Animal Unit Design

If at all possible, the design of the animal facility, with its accompanying ventilation and air-conditioning units, should be the responsibility of a specialist in the work. Section 58.43 (of Subpart C, §§ 58.41 – 51) requires the separate housing of studies with test systems or test samples known to be biohazardous, including volatile substances, aerosols, radioactive materials, and infectious agents. Ease of decontamination and cleaning, adequate separation of functions (e.g., the storage of feed and bedding away from the test areas, and the efficient handling of healthy, diseased, and dead animals are other prime objectives. This can be an expensive project, but if the design and construction are the work of experts, the money will be well spent. The concept is illustrated by the schematic layout for an animal unit shown in Exhibit 4.9. Note the separation of clean and dirty operations and the provision for animal staff to shower and change before leaving the unit. Although this is not mandatory in the GLP, no new facility should be designed without this provision. In this layout, the ventilation system would provide for air flow across the animal rooms from the clean to the dirty side, with exhaust from the building via the waste disposal area.

Additional extraction of air would be needed in the cage washing and sanitization room, to remove steam and odors.

Exhibit 4.9 Animal Unit Layout



Source: D&MD Publications.

When the facility is inspected by the FDA as part of the IND/NDA approval process, attention will be paid to the physical layout and the maintenance of the building. As advised in Chapter 6, it will be necessary to have available plans of the building showing the ventilation ductwork and means whereby cross-contamination is prevented, including SOPs for cleaning and maintenance. The manager responsible for the physical plant should attend, to answer questions posed by the inspector on this topic.

OECD: Also mentions the separation of operations involving biohazardous materials.

Japan: Includes breeding facilities in the animal care unit. It is not usual in North America to have breeding facilities in the same building as the test facilities. PAB 424 expands the short description given in Ordinance 21, Article 3. Pt 2. to cover most of the above points, including biohazard control.

Equipment (Subpart D, §§58.61–63) (OECD: "Apparatus")

Laboratory studies are increasingly depending on equipment that becomes more sophisticated and complicated with every new model. How many scientists or technicians really understand the means whereby, for example, a graph appears on the computer monitor of a capillary electrophoresis protein analyzer after the samples have been placed on the automatic sampling carousel? And, even if they understand the principle behind the operation of the machine, how many can maintain and calibrate it so as to satisfy the demands of this section of the GLP regulations? And how many scientists ever consider that the impressive new equipment just delivered to their new laboratory may not be capable of giving as accurate and reproducible a result as they were led to believe by the enthusiastic technical sales representative?

All regulations insist that the equipment used by researchers performing GLP studies must be of a ***design and capacity that will enable it to function according to the study protocol***. Weighing of samples on a mechanical balance that is accurate to 0.01 g is not permitted, when the protocol requires the sample weight to be taken to at least three decimal places (i.e., one milligram) and specifies a particular electronic balance.

Researchers are not permitted to incubate cell cultures in an incubator that maintains the set temperature +/– 0.5°C, if the virus under study must be grown at 34.0°C, +/– 0.1°C. The CFR and OEDC rules include equipment used to control the facility environment, or "for controlling factors relevant to the study," which would include the facility heating, ventilation, and air conditioning plant, as well as incubator or refrigerator cabinets and rooms. It is strongly recommended that equipment is purchased from suppliers that can support the laboratory documentation with design data, ISO 9001 compliance data and with calibration certificates for measuring instruments, containing references to national or international standards of measurement.

The location of the equipment must permit proper operation and maintenance. Strict requirements are to be found in this section of the regulations (§ 58.63) for the ***inspection, cleaning, and maintenance*** of all equipment. ***Measuring equipment must be adequately calibrated***, using appropriate standards such as certified weights and thermometers. All the laboratory standards must be supplied with the appropriate calibration certificates. All aspects of the correct operation of the laboratory equipment are to be covered by written SOPs, as described in the following section. This would include describing remedial action to be taken when equipment fails or malfunctions. Reference is usually made in the SOPs to the instructions given in the operating manuals supplied with the instruments, but possession of these alone is not sufficient to satisfy GLP.

The SOPs must describe in detail all the procedures mentioned above and specify the person (individual or unit) responsible for carrying them out. They also require the maintenance of written records of all these procedures, specifying whether they were of a routine nature, or were

performed as a result of a malfunction or failure. Then the record must state the nature of the defect and how it was corrected, with a final recalibration to demonstrate a return to proper function. A typical maintenance record is shown in Exhibit 4.10. FDA has not established guidelines for the frequency of calibration and maintenance of equipment such as balances. The manufacturer should be consulted for advice. If the routine calibration and maintenance is to be performed by the manufacturer, the relevant SOP should state that fact. It is not necessary to include the actual methods that the manufacturer's technician will use.

> **OECD**: Specifically includes "validated computer systems" and also states that "apparatus and materials used in a study should not interfere adversely with the test systems."

The FDA's requirements for the validation of computer systems are to be found in the 21CFR11 regulations, as mentioned in Chapter 3. The FDA is embarking on a re-examination of Part 11, as it applies to all FDA regulated products, and may revise provisions of the regulation as a result of that re-examination. The latest Guidance (August, 2003) explains that, while this re-examination of Part 11 is under way, the Agency will "narrowly interpret" the scope of the rule. The Guidance states that, while it is re-examining the regulations, the FDA will not normally take regulatory action to enforce Part 11 with regard to systems that were operational before the effective date of the regulation, August 20, 1997. Such systems are commonly known as existing or "legacy" systems.

With specific respect to the requirements for the validation of computer systems, the new Guidance states that FDA intends to exercise "enforcement discretion" regarding the specific Part 11 requirements for validation contained in § 11.10(a) and § 11.30. Persons must still comply with all applicable existing requirements for validation. These are principally found in the regulations governing Good Manufacturing Practice and are referred to as the "predicate rules". Even if there is no rule requirement to validate a system in a particular instance, as in the case of the 21CFR58 GLP regulations, it may nonetheless be important to validate the system to ensure the accuracy and reliability of the Part 11 records contained in the system. The decision to validate such systems, and the extent of validation, should be based on a risk analysis, in order to determine which factors in computer operations may affect the accuracy, security, and reliability of the data.

Exhibit 4.10 Typical Equipment Maintenance Record

EQUIPMENT MAINTENANCE RECORD		REF. SOP#: EM21/1
Equipment Description: Mettler Electronic Balance, 2000 g Capacity		
Model #: 123456/9 **Location: Lab. P-2/3*** **Date Installed: 7/22/00**		
Date of Service	**Procedure/By**	**Notes**
7/25/00	Initial Set-up in Room P-2 AVC	Operation validated with Standard Weights set #1.
8/23/00	Routine Calibration AVC	Set # 1: operation acceptable
9/24/00	Routine Calibration AVC	Set # 1: adjusted levels.
10/23/00	* Balance moved to Room P-3. Re-leveled & re-calibrated AVC	Set #1: operation validated.
	AVC	
7/15/01	Manufacturer's Service by: N. Bollinger NB	No major faults observed – re-calibrated with manufacturer's standards.

Source: D&MD Publications.

Critical areas for which equipment GLP compliance may be compromised are:

- Inadequate cleaning of equipment—cleaning schedules must be specified in a SOP;
- Failure to adhere to maintenance and calibration schedules and the recording thereof, as laid down in the SOPs;
- Inadequate validation of the operation and accuracy of measuring equipment and the controls of fixed environment cabinets (i.e., refrigerators, freezers and incubators). In the latter case, several certified thermometers should be placed in different sites in the cabinet to demonstrate even temperature distribution; and
- Inadequate validation of the sterilizing cycles of apparatus such as autoclaves and ovens, for which the use of unsterile solutions or instruments may compromise the study. Typical sterilizer loads containing biological test materials such as bacterial spore tubes must be run according to the recommended cycle and the absence of bacterial growth in the test tubes demonstrated after the run. Several companies supply self-contained test kits that are acceptable for this purpose. Be certain that the test samples are placed in the load so as to represent the "worst case." In the case of a steam sterilizer (autoclave) this would mean placing them where steam penetration would be most difficult and air might be trapped, so that sterilizing conditions might not be achieved. A more sophisticated validation involves the placing of multi-point recorder probes in various parts of the load and recording the temperatures in the chamber continuously during the entire run. This type of test is usually beyond the capability of a small laboratory and must be performed by a specialist outside firm. The sterilizer supplier should be able to recommend such firms. It is strongly advised that the different types of material to be sterilized in the autoclave (e.g., bottles, gowns, etc.) are arranged in standard patterns which are specified in the SOP. Each pattern will have a set sterilization cycle that has been validated as above.

In a small laboratory, the best approach to this problem is to have one experienced and capable person responsible for all routine calibration and maintenance of the equipment. The regular operators should be restricted to following operating instructions and keeping their equipment clean. They should not tinker with the apparatus, but report any possible faults to the responsible person. This person would make the necessary repairs and adjustments or arrange for them to be done by the manufacturer, and keep the records up to date. Management should ensure that this person has the tools needed for the job, including training, and sufficient time allocated in his or her work schedule to perform the tasks adequately. Time or money saved by skimping on maintenance may turn out to be very expensive in the long run, both in the cost of equipment repairs or replacement and in the risks of GLP non-compliance.

Testing Facilities Operation (Subpart E §§ 58.81 –90)

Standard Operating Procedures (§ 58.81)

In the control of the day-to-day operations of the facility and the performance of the experiments and tests for which the laboratory was set up, the writing and use of Standard Operating Procedure documents is of major importance. These documents will cover all major aspects of the facility operations and, if they are properly written, their dedicated observance will guarantee overall GLP compliance. The regulations specify that the SOPs must contain ***methods that management is satisfied will ensure the quality and integrity of the data generated in the course of a study.*** Any significant change in any operating procedure must be properly authorized in writing by the Study Director and management. QA's major role is the monitoring of a study to ensure full SOP observance.

Given the importance of the SOPs, it is advisable to expend serious effort to articulate means for creating and maintaining these in as rational and useful a form as possible. The bench-level operator must be able to understand and easily follow the SOP covering his or her work in order to be able to comply. The writing of clear, easily followed SOPs is an art, which must be acquired by those responsible for this task. A list of the minimum set of SOPs needed in the average GLP laboratory is given in Exhibit 4.11. The first of these must be "How to Write an SOP," and all other SOPs should follow the same standard layout. This enables personnel to understand the contents and instructions of a new SOP with the minimum stress. The list is derived from 21CFR58 and is intended to provide the minimum SOPs that the Agency considers necessary to assure the quality and integrity of study data. The list is not intended to be all-inclusive and should not be interpreted as such.

Exhibit 4.11 Minimum List of SOPs Required (according to 21CFR58.81)

(Items in parentheses are suggested additions)

1. Organization & Personnel

1.1 The writing, approval, amendment and use of SOPs

1.2 Ground rules for laboratory personnel

1.3 Definition of responsibilities of Study Director

1.4 Definition of responsibilities of QA Unit

1.5 Designation & duties of special staff, e.g.: Equipment Specialist

1.6 Staff records

1.7 GLP staff training

2. Facilities

2.1 Cleaning and maintenance of the facility, interior and exterior 2.2 Special cleaning & maintenance arrangements

2.2.1 Animal facility

2.2.2 Sterile operating and biohazard containment areas

2.2.3 (Validation of computerized facility systems for environmental control)

3. Equipment

3.1 Maintenance and calibration of equipment 3.2 Equipment records

3.3 (Validation of computerized apparatus)

4. Facilities Operation

4.1 Receipt, identification and storage of samples

4.1.1 Sample distribution records

4.2 Laboratory test procedures; One SOP is to be written for each procedure, including:

4.2.1 Tests on submitted test and control samples for identity, strength, purity, composition, stability, etc.

4.2.2 Formulation and testing of sample/carrier mixtures

4.2.3 Preparation and labeling of solutions and formulations, including testing of purchased chemicals.

4.2.4 Validation and operation of sterilization equipment and processes, if used

4.2.5 Operation of all specialized equipment, including biohazard or laminar-flow cabinets

4.2.6 Animal care

4.2.6.1 Receipt, quarantine, transfer, proper placement and identification of animal

4.2.6.2 Routine animal care

4.2.6.3 Receipt and proper handling of bedding, feed, etc., including periodic analyses of feed and water

4.2.6.4 Control of the use of pesticides

4.2.6.5 Disposal of animals and waste materials

4.2.7 Preparation and administration of test and control samples

4.2.8 Handling of animals found moribund or dead during study

4.2.9 Post-mortem examination of animals

4.2.10 Collection, labeling and examination of specimens (for histopathology)

5. Study Protocol and Conduct

5.1 The format of the Protocol

5.2 Amendments and revisions of the Protocol

5.3 Conduct of the Study

5.4 Recording of test data and their handling, storage and retrieval, including the use of computer-based LIMS

6. Quality Assurance Unit

6.1 Duties of the QA Unit

6.2 Establishment and maintenance of the SOP Manual and historical SOP files

6.3 Performance & reporting of study inspections & audits

6.4 Maintenance of QA inspection records

7. Records and Reports

7.1 Final report writing

7.2 Archiving and retrieval of samples, specimens and raw data

Source: Derived from 921CFR58.81.

OECD: Includes the following additional SOPs:

- Computerized Systems: Validation, operation, security, change control, and back-up.
- Room preparation and environmental room conditions for the test system.

Guide to SOP Writing

The following guidelines may assist in the writing of effective SOPs:

- Use a standard format for all SOPs—this can be based on the familiar layout used for writing scientific reports, but with certain additions or deletions, as appropriate (See Exhibit 4.12):

  - Title (e.g., "The Calibration of pH Meters") with Version Number
  - Date of original version and author
  - Dates of any revisions and authors
  - Record of the approval process for each version
  - Short Description of the Procedure (e.g., "This SOP describes the routine calibration of pH meters in the facility using the standard buffer set # 123/4.")
  - Materials needed: Apparatus used, chemicals, cleaning solutions, tools, control samples, reference standards, etc.
  - Methods: Note the need to provide adequate safety instructions. The description of the procedures should include: when the procedure is to be applied; the exact description of all stages of the procedure; the data to be recorded; the check points; the records to be kept; the standards to be complied with, etc.
  - Result to be reported: this could be as little as "Calibration showed no deviation," or with details such as "Potency calculated as 416 units/mg, with Standard calculated at 105 U/mg—within acceptable limits."
  - Conclusion: Could be a simple statement, such as "Test Passed" or may indicate further action, such as "Equipment to be sent for repair due to inability to calibrate properly."
  - Dated Signatures: of operator and countersigned by supervisor.
- Be as brief as is consistent with understanding.
- Include any references to published reports, pages or sections in equipment manuals, etc. that will support the SOP. It is permissible to state "Follow start-up and operating instructions given on pages 3–6 of the operating manual, version 3.4", rather than copying these instructions verbatim.
- Set up a system whereby the original SOP is drafted by someone familiar with the procedure or responsible for the function, using the recommended format. This draft should then be reviewed by a more senior operator or supervisor to confirm the accuracy of the instructions.
- Pass the reviewed draft to the QA representative, who will ensure adherence to the correct format and will then take the SOP through the rest of the approval steps, resulting finally in the listing of the approved original in the Master SOP Manual and the issue of authorized copies to users.

Exhibit 4.12 Templates for SOP

STANDARD OPERATING PROCEDURE: LABORATORY OPERATIONS			
COVER SHEET	**SOP#_ LO.xx.xx**		
Originated By:	**Date:**	**Effective:**	
APPROVALS			
Supervisor:	**Date:**		
QA Manager:	**Date:**		
CEO or Senior VP:	**Date:**		
REVISIONS			
#1: By:	**Date:**	**Effective:**	
Supervisor:		**Date:**	
QA Manager:		**Date:**	
CEO or Senior VP:		**Date:**	
#1: By:	**Date:**	**Effective**	
Supervisor:		**Date:**	
QA Manager:		**Date:**	
CEO or Senior VP:		**Date:**	
(Continue on Additional Sheets)			

STANDARD OPERATING PROCEDURE: LABORATORY OPERATIONS	
PROCEDURE DESCRIPTION	**SOP# LO.xx.xx**

1.0 Title:

2.0 Purpose & Scope

2.1 Purpose of Procedure

2.2 Scope of Procedure

3.0 Responsibilities

3.1 Operator responsibilities

3.2 Supervisor responsibilities

4.0 Principle of Test (if applicable)

5. 0 Reference Documents

5.1 Other SOPs

5.2 Other laboratory references

5.3 Journal references

6.0 Materials and Equipment

6.1 Sample/specimen Description

6.2 Chemicals and Reagents

6.3 Equipment

7.0 Procedure

7.1 Safety Precautions

7.2 Special handling procedures

7.3 Calibration of analytical equipment

7.4 Test Steps

7.4.1 Step 1

7.4.1.1 Sub–step 1 of 7.4.1

7.4.2 Step 2…etc.

7.5 Test acceptance criteria

7.6 Data to be recorded

7.7 Records to be retained

7.8 Disposition of reserve samples or specimens

8.0 Data Analysis, Calculations, etc. (if any)

9.0 Reporting of Test Result

10.0 Test Conclusion (if any)

11.0 Attachments, Forms

Source: D&MD Publications.

- Copies of the approved SOP are to be provided to all laboratories that might be performing the procedure. The laboratory manager must ensure that a copy of the current version is available to an operator at all times and that the operator is familiar with the SOP and is observing the instructions. It is best to have the laboratory copy bound in clear plastic covers to protect it on the bench. It will be of no use if it has to be kept in a drawer or is illegible. Any operating manual or published report also referred to is to be in this place as well.
- Once the SOP is listed in the Master SOP File, any further amendments may be suggested by an operator or required by senior management, but in each case the amended document must go through the same approval process before replacing the original. It is then the QA's responsibility to assure that all issued copies of the SOP are the latest version. All previous copies are returned to QA and destroyed, except for one Master File copy and one back-up, both of which may be electronic. In other words, the Master File will contain all approved versions of any SOP, in date order, so that amendments can be traced back and explained.

There are other published guides and sample formats for the writing of SOPs. Some of these are listed in Chapter 8—References and Further Reading. These do not, however, substitute for the work that must be done in the test facility to ensure that an SOP clearly defines all steps of a procedure which assures the accuracy and integrity of the data that the procedure generates or maintains the facility and equipment in a state that assures the correct conduct of a study. As a piece of research is eventually judged on the basis of the published report, so the quality of a GLP facility is judged on the efficiency of its SOP system.

Finally, the SOP Manual will be an invaluable aid in the transfer of technology from the facility to an industrial partner or contract laboratory that may perform some of the drug development program, or to the work of the regulatory consultants who may assist in the assembly of the IND or NDA documentation.

Reagents and Solutions (§ 58.83)

The *correct labeling* of reagents and solutions in the laboratory area attracts a special mention in the GLP regulations. A correct label (Exhibit 4.13) includes information on the identity of the solution, whether the contents are sterile, titer, or concentration, storage requirements and expiry date. This is an area often cited for noncompliance in inspection reports. FDA believes that expiry dates should be required on all reagents and solutions, without regard to their stability, so that there is no doubt about the suitability of the material for use. Don't forget that purchased reference reagents, which may be dispensed into smaller bottles from the original package, should be similarly labeled.

Management should create and issue a ***standard self-adhesive label*** on which all the required information can be written. The SOP on labeling of reagents and solutions should specify that only this label is to be used on any storage container. In the case of standard solutions such as buffers, which are regularly prepared and used in the facility, it is advisable for QA to issue preprinted labels which will only require the preparation and expiry dates to be written in. The SOP for the preparation of these solutions would include instructions to use only the pre-printed labels.

All chemicals and reference standards should be purchased from accredited suppliers who are prepared to provide certificates of analysis and, where appropriate, evidence of compliance with the national pharmacopoeia and other compendia or formularies. OECD has a guideline on the qualification of suppliers, ENV/JM/MONO(99)21, which was revised in 2000. This should be reviewed by the laboratory purchasing manager.

Exhibit 4.13 Solution Label

I.D.:	**Date Prep:**
STERILE/NONSTERILE	
Concn./Titer:	**By:**
Store at: RT/4°C/-20°C/-80°C	**Exp:**

Source: D&MD Publications.

Animal Care (§58.90)

As shown in Exhibit 4.11, SOPs are required to be written for all aspects of the handling and care of animals used for non-clinical GLP tests. Particular attention should be paid to the following aspects of this function:

- Ensuring that all animals supplied are from accredited dealers who are able to provide comprehensive information on the strain, substrain, and breeding history of each lot supplied. The breeder should, ideally, also provide a veterinary certificate of health issued on release of the lot to the facility.
- Isolation, veterinary examination, and any necessary quarantine of newly received animals to ensure their freedom from disease before use. The entry of any diseased animal into a study is prohibited.
- Isolation of any animals showing signs of illness during the study. These animals should be appropriately treated for any signs of disease, provided the treatment does not interfere with the study. If the disease condition does not satisfy this criterion, the study must be stopped, the animals treated or euthanized and autopsied as necessary. The study will then be repeated with fresh animals. All observations, diagnoses, and treatments are to be documented and the records retained as part of the study data.
- ***Proper labeling of animal cages and identification of individual animals*** that must be removed from their cages during the study, or that might escape during normal handling. Tattooing, usually of an ear, or indelible coloring of some part of each animal is one way of dealing with this. There are also electronic labeling devices available, which read a code from a small implant. These are the most reliable.

The cage label should identify individually and clearly every animal housed there, using the same code (Exhibit 4.14). Note that, ***if the cage label eventually contains a test observation*** (e.g., to indicate the removal of a dead or moribund animal) then all the labels must be kept as part of the raw data of the study.

Exhibit 4.14 Animal Cage Label

Study#:	**Date Start:**
Sample ID:	**Route:**
Species:	**Number:**
Animal Code:	
1.	**7.**
2.	**8.**
3.	**9.**
4.	**10**
5.	**11.**
6.	**12.**

Source: D&MD Publications.

To illustrate a QA nightmare: A story is told of the animal technician who accidentally dropped a box containing 100 white mice during their unauthorized transfer by passenger (not freight) elevator from the receiving dock on the ground floor to the test laboratories on the top floor of a multi-story office/laboratory building. As the elevator stopped automatically at each floor the doors opened, a certain number of small white rodents exited, and then the elevator proceeded to the next floor where the scenario was repeated. The final mouse count on arrival at the top floor was 15. The comments of the human passengers or of the building management were not recorded. This actually happened !

- The housing of different animal species in separate rooms when necessary. Adequate separation is also needed of groups of the same species used in different studies running at the same time, where any accidental exposure to a test substance or a mix-up could invalidate a study.
- Adequate cleaning and sanitization of animal cages, racks, and accessory equipment.
- Periodic analysis of animal feed and water to ensure the absence of any substances known to interfere with the study that may reasonably be expected to be present. The protocol should specify the maximum permissible limits of such contaminants. The analyses should be preserved as part of the study raw data. The suppliers of the feed should be prepared to

provide these data on a regular basis, or the analyses must be done in-house.

- The use of bedding that does not interfere with the conduct of the study and the changing of the bedding as often as necessary to keep the animals clean and dry.
- Documentation of the use of pest control materials and avoidance of the use of any cleaning or pest control chemical that might interfere with the study. Again, the suppliers of these materials should cooperate with the facility to ensure compliance here.

The most complicated and expensive part of the pre-clinical studies is always the animal testing. The maximum effort should be put into ensuring that the animal tests are done correctly and in compliance. Then the dreaded words "test must be repeated" will not be heard and the project will be on schedule and under budget.

OECD: Includes a mention of physical/chemical test systems, as well as biological. The equipment to be used in such test systems is qualified as under "Apparatus" and "the integrity of a physical/chemical test system should be ensured." Special attention must be paid to computerized laboratory equipment. In these cases, the operation of the computer software must be validated to demonstrate that accurate, reliable results are regularly produced. This topic is discussed in the "Electronic Data Management" section of this Guide.

Test and Control Articles (Subpart F, §§ 58.105–113) (OECD: "Test & Reference Items")

This section refers to the samples to be placed on test and any used as controls in the same test. GLP requires that these are properly characterized and labeled so that confusion or mistakes are minimized.

Characterization depends on establishing which tests will properly define the sample, especially identity, strength (i.e., concentration, potency or biological activity) and composition of formulations or mixtures. These characteristics are determined for each sample before the study proper begins. They are documented by some form of Certificate of Analysis and this may be supported by actual laboratory data, such as chromatograph printout. A similar range of tests must be performed on every batch of samples submitted for testing.

If the tests used for characterization are not published in official compendia, such as the U.S. Pharmacopoeia, but will be described in official submissions, they are required to be validated. The validation of analytical procedures is described in Guidances published by FDA and ICH, referenced in Chapter 8. Basically, a valid analytical method is performed using qualified equipment, shown to be suitable for the intended use, and methods shown to yield accurate, precise, and reproducible results. Repeat testing of known standard preparations and test samples are performed, to collect sufficient data to enable reliable statistical analyses of the results to be performed. Further information on validation techniques is available in D&MD's *Guide to Good*

Validation Practices.

It is also necessary to identify clearly the ***manufacturing stage*** and origin of the sample and to document its method of synthesis, fabrication, or derivation. This information should be documented by the originating laboratory or study sponsor and received by the study laboratory at the same time as the samples. It may be sufficient to summarize the information on the Certificate of Analysis, as shown in Exhibit 4.4, but often additional documents must be supplied and these should be noted and incorporated in the study file at the time of receipt.

If ***control samples*** for the study are marketed products, such as an approved drug with which a new compound is to be compared, the regular approved labeling of the control drug will be considered sufficient documentation to characterize this.

Studies may run for several months and loss of activity or unrecognized changes occurring during prolonged storage may affect the behavior of the material in the test systems or distort the pharmacological and toxicity findings. It is essential that the ***stability of the samples*** under test is known. If this information is not available at the start of the study, stability tests may be run concurrently with the study. A written SOP must specify the periodic sampling and assay of samples stored at different temperatures. Unless the stability of the product is known at the start, the samples needed for later application during the study should be stored at as low a temperature as is considered advisable and shielded from light. Note that the expiry date printed on the label of a marketed drug used as a control will not be sufficient for this purpose. FDA requires that stability tests are performed on both test and control articles.

Each of the sample ***containers*** (e.g., bottles, vials, or packages) must be clearly labeled with the following information: Name, chemical abstract number or code number, batch number, expiration date, if any, and storage conditions for maintenance of optimum stability (See Exhibit 4.15). The label of an article that is under concurrent stability test should carry a reference to that test, since an expiry date cannot be given. The operator should refer to the current data from the stability test to determine whether the article can continue to be used.

Exhibit 4.15 Sample Container Label

Test* Sample ID:	**Date:**
Code #:	**Study:**
Store At:	**Entry Date:**

* OR "CONTROL"

Source: D&MD Publications.

All the samples from one batch should be housed in one or more dedicated containers, such as a metal box with lid and internal partitions, which should be labeled with the sample information, as well as the number of sample containers originally received and a record of the date, destination, and number of samples issued during the study.

The box must be dedicated at the start of the study and all unused samples returned to it, so that a proper audit of sample distribution can be made at the end (Exhibit 4.16). A test article may not be transferred to different sized storage containers as a study progresses, nor may assigned containers be destroyed or used for other materials while a study is in progress. FDA considers that the mere act of transferring a test article from one storage container to another introduces the opportunity for contamination of the test article by other laboratory materials or for mix-ups to occur.

The same information should be entered into a sample record book, which forms part of the study documentation. QA will, as part of the study monitoring process, check that the number of samples contained in the box corresponds with the label and the record book and that ***all distributed samples can be accounted for***. Reserve samples may be accessed for test repeats, at the authorization of the SD, but sufficient reserves must be left, so that the batch samples are not exhausted. For studies of more than four weeks' duration, reserve samples from each batch of test and control articles are required to be retained for the period of time provided by § 58.195 (see Records and Reports Section).

If the study requires the incorporation of the sample into a carrier, such as a feed, or it is to be mixed with for example an adjuvant preparation, the final formulation should be tested to ensure proper mixing and even distribution of the sample and its concentration in the final mixture. In the case of samples of poor stability, additional stability tests will be required on the mixture to be

carried out before or concurrently with the study. If the final formulation contains ingredients that have an expiry date, this must be shown on the container label. If more than one component has an expiry date, the earliest is shown.

Critical non-compliance factors in this part of the regulations are usually concerned with poor labeling and the control and documentation of sample receipt, storage, and distribution. Attention should also be paid to the necessity to repeat, or to have documentation of, the characterization testing on every batch of samples received, even of the identical material.

Exhibit 4.16 Sample Storage Box Label

Test/Control Sample ID:			**Date Rcvd:**	
Store At:			**Expir. Date:**	
Code #:	**Study #:# of Cont:**			
Issues:	**Date**	**Quantity**	**To**	**Balance**
Returns				

Source: D&MD Publications.

Protocol for and Conduct of a Study (Subpart G, §§ 58.120–130)

The Study Protocol (§ 58.120) (OECD "Study Plan")

This document will form the framework on which the study is built. It must be written in its entirety, following an outline such as this:

- Title and purpose of study

- Identification of the test and control articles by:
  - name
  - chemical abstract number, or
  - code number
  - reference to the originating laboratory's experimental program
- Name of sponsor or originating laboratory
- Name and address of the facility at which the study is being done
- Proposed start and completion dates for the study
- Description of test systems
  - In vitro tests for characterization of the samples, especially:
    - Identity
    - Potency/concentration
    - Purity
    - Homogeneity
    - Stability, including any ongoing stability test program
  - In vitro tests for safety or toxicity, e.g. in cell cultures
  - For in vivo safety/toxicity tests:
    - Species of animal
    - Strain, substrain
    - Source
    - Number in each group
    - Body weight
    - Sex
    - Age
  - Identification methods for test systems—cage codes, etc.
  - Experimental design, including means for avoiding bias
  - Definition of diets and any materials used in formulations
    - Includes specifications of acceptable levels of expected contaminants
  - Dosage regimen, in mg/kg of body weight or other appropriate units and schedule of dosage
- Type and frequency of the tests to be applied, analyses and measurements to be made.
- Records to be maintained (This is in addition to the requirements in §§ 33, 190 and 195 for record maintenance, since the FDA considers that the protocol is the reference document for all involved in the study).
- Statement of the statistical methods to be used in analyzing the results. This is considered by

FDA to be part of the experimental design, so that the methods should be specified up front, even if they will need modification later.

- Date of approval of the protocol by:
  - Sponsor or originating laboratory
  - Test facility management, with Study Director's dated signature

The protocol should also include references to all SOPs to be followed in the conduct of the study. Any changes in or revisions of an approved protocol made during a study must be documented, with the reasons for the changes and the records of these signed and dated by the Study Director. These documents then become part of, and are maintained with, the protocol.

OECD: Also requires that the Study Plan contain the addresses of the Sponsor and Study Director (and Principal Investigators, if any).

The proposed dates of start and completion of the study should also be stated.

Japan: (PAB 424) Requires that the Study Director is responsible for compiling the study protocol.

The reason for selection of a particular test system should be stated.

The animal feed to be used is identified by name and code number, as are all carriers, emulsifiers, etc. to be used in conjunction with the administration of the test article.

The reason for using a particular route of administration is to be given.

Conduct of the Study (§ 58.130)

Here the GLP regulations mandate that the study must be performed in accordance with the approved protocol and any changes or revisions thereto. The test systems used and their observation and monitoring must also be according to the protocol, and should comply with the specified SOPs for the conduct of the tests.

Other points to be observed in relation to the study conduct:

- The study must have a unique identifying code, which must be carried by all records and labels.
- Specimen labeling. All specimens taken during animal tests must be identified by test system, study, nature, and date of collection (See Exhibit 4.17). These characteristics are considered to be the minimum information needed to distinguish a specimen.
- Specimen pathology. The records of any gross findings for a specimen from autopsy observations should be available to the pathologist who is examining the histopathology of the specimen, unless the examination is to be "blinded."

Exhibit 4.17 Label for Specimen Container

Study ID:	**Test System:**
Species:	**Animal Code:**
Specimen:	
Date Taken:	

Source: D&MD Publications.

Recording of Data

This is a critical issue and has already been mentioned in the Ground Rules for the laboratory (Exhibit 4.2). It is mandatory for the records of any experiment or test ***to be made promptly and directly***, usually into a permanent record book or onto a multiple-copy form, one copy of which is then bound into a permanent record. The transfer of raw data from loose-leaf notes to a bound notebook is not recommended, as it has been identified as a common source of error. ***All entries must be in permanent ink and must be legible***. This requirement may create problems in even the best-run laboratories, given the lack of proper hand-writing training in our schools. If there is any question that an entry may not be legible, the operator must be instructed to use only capitals—many people become very adept in writing in "small caps" for records.

All entries are to be dated and signed or initialed by the person entering the data. ***Any changes in the entry must be made so as not to obscure the original entry***. This is an area where non-compliance is extremely common. No "white-out" inks or erasure is allowed.

The entry that needs to be corrected is simply ~~struck through like this example~~, so that it can still be read, and the revised text or figures written next to or above the original. For this reason, it is advisable to ensure that the spaces on pre-printed forms are large enough to permit this type of correction. Or, special spaces for revisions can be designed on the form. Operatives should be advised to use double spacing when working in bound notebooks. The reason for the change should also be inserted and the correction initialed and dated. Although not mandated by GLP, most laboratories also require that all record entries are counter-signed by a supervisor at the end of the working day. This is an excellent check of the accuracy of data entry and can prevent errors from being overlooked. It also provides a means of protecting data that may be needed to form part of a patent application.

Any charts or print-out from laboratory equipment that form part of the test data should be permanently fixed to a page of the record book or bound into the master copy. It is advisable to sign and date across the insert to show that it was not added later or moved.

Electronic Data Management

According to the new Guidance, under the narrow interpretation of the scope of 21CFR 11, with respect to records required to be maintained or submitted, when persons choose to use records in electronic format in place of paper format, Part 11 would apply. On the other hand, when persons use computers to generate paper printouts of electronic records, those paper records meet all the requirements of the applicable predicate rules, and persons rely on the paper records to perform their regulated activities, the merely incidental use of computers in those instances would not trigger Part 11. In such instances, FDA would generally not consider persons to be "using electronic records in lieu of paper records" under §§ 11.2(a) and 11.2(b).

With the increasing use of computers to calculate and display data from analytical equipment and of computer-based ***laboratory information management systems (LIMS)*** for recording and handling data, the regulations have specific requirements for "automated data collection systems". In LIMS, each person responsible for the direct input of original data must be identified at the time of data input. This is usually achieved by a system whereby access to the specific data form is restricted to certain authorized persons, who use a unique identifying code. Input of the code and a password automatically records the access by that person, and provides a time/date stamp to each entry. Again, the computer forms must be designed so as to allow changes to the original entry without obscuring or deleting this. It is highly recommended that a supervisor or the system manager be appointed to countersign all entries to confirm that correct procedures are being followed and that the password system is secure. Note that, if the data are originally recorded on paper and then transferred to electronic records, the raw data are considered to be the original paper records, so these must be preserved.

SOPs must be written to cover all aspects of data recording and handling, as suggested in Exhibit 4.10. These should include the purpose of any particular computer program, the specifications, procedures, end products, language, and interactions with other programs and procedures for authorizing and making any changes to the programs. In the case of data generated and recorded by electronic means (i.e., directly by computer-controlled analytical apparatus) either the contents of the magnetic media (disks, back-up tapes) or the hard-copy printouts are considered raw data and must be suitably archived.

> **OECD:** Provides a very useful definition of the means of handling computer-entered data. It states "computerized system design should always provide for the retention of full audit trails to show all changes to the data without obscuring the original data. Electronic signatures should be timed and dated."

The FDA's 2001 manual for bioresearch monitoring inspectors includes instructions to inspect computer systems for documentary evidence that the following procedures are in place:

- Validation study, including validation plan and documentation of the plan's completion. (The decision to validate a particular system should be based upon a risk analysis.)
- Maintenance of equipment, including storage capacity and back-up procedures.
- Control measures over changes made to the computer system, which include the evaluation of the change, necessary test design, test data, and final acceptance of the change.
- Evaluation of test data to assure that data are accurately transmitted and handled properly when analytical equipment is directly interfaced to the computer.
- Procedures for emergency back-up of the computer system (e.g., back-up battery system and data forms for recording data in the event of a computer failure or power outage).

Records and Reports (Subpart J, §§ 58.185–195)

The entire validity of the work performed in a GLP facility will depend eventually on the accuracy and completeness of records kept and the reports written, based upon these records. The generation of the records of test data has already been dealt with. This section is concerned with the writing of the final report, the storage and retrieval of all raw data, documentation, and specimens to be retained and the long-term retention of records.

The Final Report of the Study (§ 58.185)

A Final Report is prepared for each study, usually by the Study Director, or at least under his or her direct supervision. The format for this report is articulated in this section of the regulations and it generally follows the format defined for the Study Protocol.

The following headings are a minimum for this report:

- Name and address of the facility, the study director, and any Principle Investigators at other sites.
- Dates on which the study was initiated and completed.
- Objectives of the study and procedures used, as detailed in the protocol.
  - Any changes in the original protocol should be detailed here.
- The statistical methods used for analyzing the data.
- Full specifications and characteristics of the test and control samples used in the study.
  - Give name, chemical abstract number or code number.

  - Give data on purity, strength, composition, etc.
- The results of the stability tests of the materials under study, demonstrating the satisfactory stability of the samples under the test conditions.
- Description of all methods used.
- Description of test systems, especially in vivo systems. In the latter case, details will be given of the species, strain/substrain, and source of animals used, their number, sex, body weight range, and identification procedures (e.g., implant, tattoo).
- Description of the use of the animal test system, including the dosage of the test and control samples, the dosage regimen, route of administration, and the duration of the procedure.
- Description of any observed circumstances which may have affected the quality or integrity of the data.
  - It is here that the SD and QA Unit must show that they were aware of any occurrences that might have compromised the test and provide documentation of their dealing with the matter and what effect they expect it to have had upon the responses of the test system.
- The names of the study director, scientists and all supervisory staff involved in the study. FDA considers that supervisors play an important role in the data collection process and the accountability of these persons must be assured.
- A description of all statistical manipulations performed on the data, a summary and analysis of the data, and any conclusions drawn from the analysis.
- The signed and dated reports of each of the individual professional investigators or contributing scientists involved in the study.
  - e.g., Veterinarians, pathologists, microbiologists
- FDA considers that reports from scientists of different disciplines should not be combined in the final report. Each individual scientist involved in a study has to be accountable for reporting data, information, and opinions within their area of expertise or designated area of responsibility.
- Description of the archives (i.e., the locations where all specimens, raw data, individual reports, and the final report are to be stored).
  - It is probably advisable to include in this section the name(s) of those responsible for the control of the archives.
- The Quality Assurance Statement, as specified in Section 4.1, which will describe:
  - The inspections performed on the study;
  - The dates the inspections were made; and the findings of non-compliance, if any, were reported to management and the SD;
  - The findings reported to management and the SD of non-compliance, if any, and the

remedial action taken; and

- Confirmation that the report accurately reflects the raw data generated by the study.

- Signature and date of the study director. This is the formal completion date for the study.
- Any corrections or amendments to the final report These must be made by the SD, clearly identifying:
  - The part of the final report that is being corrected or amended; and
  - The reasons for the changes, with signatures and dates of the person responsible.

The final report should be written as soon as all the relevant reports and data have been received. A report that has been prepared meticulously according to this outline should be acceptable as part of a formal submission to the FDA for an IND or NDA without any additional work. Thus, the more time and effort spent in getting this right in the first place, the fewer the problems encountered later, when the scientific data and conclusions may not be so fresh in the minds of, or familiar to, the people preparing the documentation from the original data.

Archiving the Data (§ 58.190)

In order to support the final report and regulatory submissions based upon it, and to enable further analysis of the study if required, it is essential and mandatory that all raw data, documentation, final reports, and specimens be maintained in secure archives. The only material excluded from this requirement in the CFR are "wet" specimens, such as blood, urine, and biological fluids and any specimens obtained from mutagenicity (teratogenicity) tests. These latter could include cell cultures used to study in vitro cell transformation, as well as animal specimens.

All this material must be maintained in archives that allow orderly storage and rapid retrieval of data or specimens. Thus, a system of filing of the archived data must be in place and SOPs written for these functions. The place of archiving must ensure that the stored materials will not deteriorate over the time period that they are required to be kept. This means dry, cool conditions, preferably in locked, fire-proof cabinets or similar. It is worth determining whether there are any stray magnetic fields, such as from high-voltage cables or electrical equipment,that might compromise the integrity of records held on magnetic media. Some specimens may need to be kept in locked refrigerators or freezer cabinets. It is permissible for the testing facility to contract with an outside commercial organization for the archiving, and for raw data and specimens to be stored in other locations, provided that the archives contain reference to these other locations.

Management of the facility must designate an individual to be responsible for the archives. This person will maintain the records of locations of all archived data and materials and should also ensure that only authorized personnel have access to these. The regulations further specify the indexing of the archived materials for easy access and retrieval. The key words in this regulation are "***orderly storage and expedient retrieval***." FDA inspectors have on many occasions referred in

their reports to difficulties in accessing original laboratory data and specimens in order to audit the study records or to check some point needing clarification in an IND or NDA document. Inability to provide expedient retrieval of the data will markedly delay the approval of the submission and, in extreme cases, may result in a request for a particular study to be repeated.

Retention of Archived Records and Specimens (§ 58.195)

The CFR specifies the length of time that different types of study records, reports, and specimens are to be retained in the archives. These are laid out in Exhibit 4.18. Apart from the actual archives, other laboratory records, created as required by these regulations, must be maintained for similar periods by the responsible departments. These are listed in Exhibit 4.19.

Form of Retained Records (§ 58.195 g)

Written records may be kept either as originals or, better still, as "true copies." A "true copy" means photocopies, microfilm, microfiche, or other accurate reproductions of the originals. It is highly recommended that, if the original documents are maintained in some remote, secure situation, then micro-files are kept on site for easier reference. There is also the possibility these days of scanning all documents into computer files which may then be transferred to "magnetic media" such as removable discs or tape records or "burned" onto CDs. These simplify storage and retrieval considerably and the method is being employed more frequently. It is worthwhile to check whether the storage site for magnetic media is free from extraneous magnetic fields, such as high-voltage cables or electrical equipment, that might compromise the records. In this respect, files on CDs are more stable.

Exhibit 4.18 Retention Times for Archived Materials

Description of Materials	Retention Period
All data, reports and specimens from a study which forms part of an application for Investigational New Drug clinical research or New Drug Approval for marketing	5 years from date of submission of IND or NDA
Other situations, i.e., where the study in question does not form part of an IND or NDA application	2 years from date on which the study was completed, terminated or discontinued
Wet specimens (apart from biological fluids and specimens from mutagenicity tests), samples of test and control materials and any specially prepared materials which are unstable or fragile.	Only as long as the nature of the material allows evaluation, but no longer than that set out above.

Source: Derived from 21CFR 58 (USA).

Exhibit 4.19 Other Records to be Maintained

Responsible Department	Records to be Maintained
Personnel Management	Summaries of staff education and training, experience and job descriptions, as detailed in Section 4.1 (§58.29)
Quality Assurance	Master schedules, copies of protocols and records of QA study inspections, as detailed in section 4.1 (§58.35)
Equipment Supervisor	Records and reports of the maintenance, inspection and calibration of all equipment, as in Section 4.3 (§58.63)

Source: Derived from 21 CFR 58 (USA).

Transfer of Records (§ 58.195h)

The CFR acknowledges the fact that a commercial laboratory conducting non-clinical studies may go out of business and the question of the disposition of retained records will then arise. The regulations then require the records to be transferred to the archives of the sponsor of the study. In the case of a university spin-off company that closes, it is the university that will then have to arrange for the suitable storage of the archives and appoint a curator. In all cases, the FDA must be informed of the transfer, of the new site for archive storage and the name of the individual now responsible for the archives.

Conclusions

This analysis of the critical areas of the regulations has been fairly exhaustive, and following these recommendations should provide an easy way to achieving compliance. Attention to the details of SOP writing and the conduct of the study must always be emphasized, but ***the main conclusion to be drawn is that, if a research laboratory is new to the GLP concept, there may need to be a radical change in attitude*** on the part of the management and the staff of the laboratory.

University researchers and their technical assistants are always looking for a better way to study something, or to perform a particular experiment. Many of the advances in biotechnology science have occurred in the technical area. It is possible now to perform genetic manipulations and molecular engineering feats that were unthinkable a few years ago. But, when a protocol has been

written and a GLP study is about to start, all thoughts of "Let's try it and see..." must be banished from the minds of the staff. Each SOP referred to in the protocol will reflect the best method that was available at the time of writing and that is what the staff must follow. "Creativeness" is to be placed in abeyance—it has no place in the observation of Good Laboratory Practices. With this thought firmly in mind, we can now move on to consider the actual submission of the data to the Regulatory Authorities, usually in the form of an Investigational New Drug (IND) submission to the FDA or Clinical Trial Application (CTA), as it is known elsewhere.

CHAPTER 5: SUBMITTING PRE-CLINICAL STUDY FINDINGS IN CLINICAL TRIAL APPLICATIONS

Although the contents of this chapter do not refer directly to the GLP regulations, it is advisable to discuss the way in which the data generated by GLP studies are to be presented to the FDA and other regulatory authorities, especially since the rules for IND submissions are in the process of changing. Until July 2003, the FDA's regulations governed the contents and format of submissions, especially those for marketing approval. New Drug Applications (NDA), Abbreviated New Drug Applications (ANDA), and Biological License Applications (BLA), were governed by the rules contained in 21CFR 314 and 21CFR601. The form and content of IND applications were similarly controlled by 21CFR3 12, § 23.

The rules were amended following the issue by ICH of the specification for the Common Technical Document (CTD) as part of the harmonization of technical requirements for registration of pharmaceuticals for human use. The CTD will replace those sections of drug marketing approval applications that cover the quality, safety, and efficacy aspects. The content of the CTD does not differ much from that defined by CFR, but the document's organization and format are very different. Beginning in July 2003, all new drug applications in Europe and Japan will have to contain the technical information in CTD format. In the USA, the FDA is accepting electronic submissions for INDs and NDAs in the CTD format, and it would make sense for a paper submission to use the same guidance. Other countries, such as Canada and Australia have followed suit, in fact Canada now requires all CTAs to be in the CTD format.. The following sections examine the rules that were in existence for the formatting of INDs in the USA, and the way that these may be changed by the use of the CTD.

IND Contents According to FDA

21CFR3 12, section 23 defines the content of an IND. Two Guidances to Industry, issued in 1995 and 1999 and 2000, respectively, gave recommendations for the organization and content of INDs for Phase 1 and Phase 2/3 studies.

In general terms, an IND is supposed to contain a description of the drug substance (active ingredient) and the drug product formulated to deliver this. Adequate information has to be provided on pharmacological and toxicological studies in laboratory animals or in vitro to support a sponsor's conclusions that the drug is safe to be studied in trials in human subjects. The remainder of the application is concerned with the proposed clinical trials.

The IND should contain a description of the pharmacological effects of the drug

(pharmacodynamics, PD) and its adsorption, distribution, metabolism, and excretion (pharmacokinetics, PK) in animals. Toxicology studies should be presented in an integrated overview, supplemented by a full tabulation of the data from each individual study. For those studies considered to be subject to the GLP regulations contained in 21CFR58, a statement is required that each study was performed in compliance with the regulations, or, if it was not in compliance, a brief statement of the reasons for noncompliance is required.

Naturally, the requirements for characterization of the drug according to set specifications and validation of the manufacturing processes and analytical methods used in its production and characterization become more stringent as drug development proceeds. Thus, the 2000 guidance entitled *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products* states that validation data and established specifications need not be submitted at the initial stage of drug development. However, for certain well-characterized biotechnology products some preliminary specifications and validation data may be needed for safety purposes.

For Phase 2 studies, the 1999 guidance INDs *for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products*, which deals with the chemistry, manufacturing, and control sections of the IND, states that the analytical procedures used to support acceptance criteria should be described and supporting validation data for tests not described in official compendia "should be available on request." By the time the product is to be entered into the Phase 3, pivotal, studies, the IND must contain a complete description of non-USP analytical procedures with appropriate validation information. These data should delineate such test parameters as accuracy, precision, and specificity, with detection and quantitation limits defined.

With the exception of the tabulated results mentioned above, there is virtually no indication in 21CFR3 12.23 of the actual document organization to be used in creating the IND. This has led to the use of many different formats in documents submitted to the FDA. In addition, the different requirements that existed in the other members of the ICH meant that most IND applications had to be rewritten when trials outside the United States were considered.

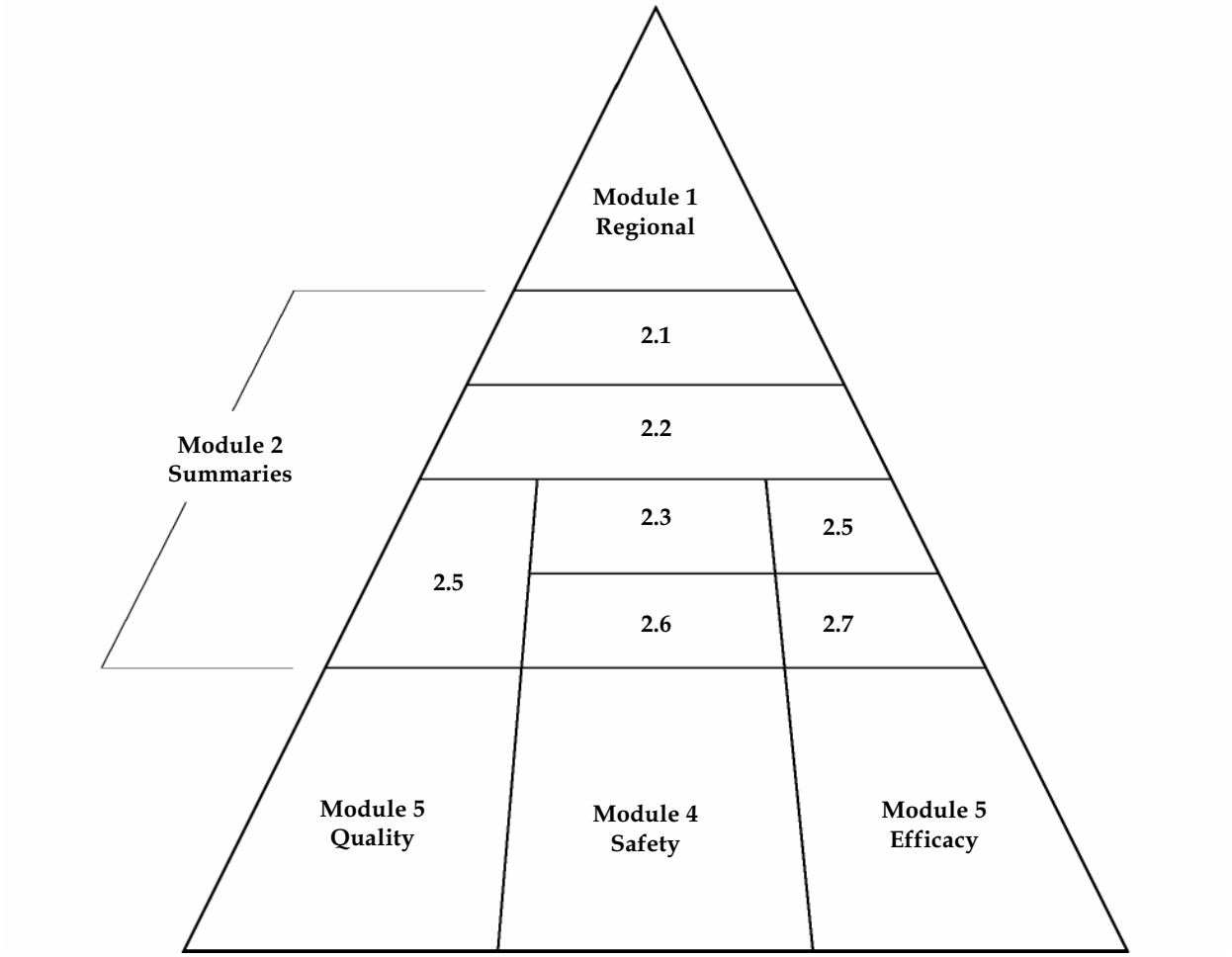
So, although the CTD guidance is intended to harmonize the requirements and provide a common format for all applications to market a new drug, it is probably a good idea to use the same layouts and formats when preparing technical documentation for an application for clinical trial approval. It is likely that much of the same pre-clinical data will appear in both the IND and the eventual NDA, so it will save a considerable amount of work if the pharmacology and toxicology study reports are summarized and tabulated according to CTD guidelines from the start. Certainly, an IND containing data presented in CTD format will not be sent back for re-writing. As more laboratory and animal data are developed through the phases of the clinical study, these can easily be incorporated into existing tables.

The ICH Common Technical Document

The original format of the CTD was developed by a multinational Working Group and finally published for adoption by ICH members in November 2000. After the ICH meeting of September

2002, some revisions were issued to improve consistency and permit the development of an electronic form of the document. The CTD format and organization are presented in a series of four documents, known as the CTD guidances. The contents are illustrated in Exhibit 5.1.

Exhibit 5.1 Contents of the CTD



Source: International Conference on Harmonization (ICH).

In the summer of 2001, the FDA published these four documents in the Federal Register, plus a general guide. These are listed here; the content of each of the four ICH papers is given in parentheses.

- *Submitting Marketing Applications According to the ICH-CTD Format – General Considerations*
- M4: *Organization of the CTD (General Information)*
- M4E: *The CTD – Efficacy (Clinical Data)*
- M4Q: *The CTD – Quality (Chemistry, Manufacturing & Control)*
- M4S: *The CTD – Safety (Preclinical data)*

There were a few later revisions, as described above. Subsequently, in 2003, a guidance on the creation of an electronic form of the CTD, the "eCTD," was published. The CTD is organized into Modules on the same basis as the guidances and within each module (except Module 1) the format of the data to be presented is laid down.

The Modules are:

1) Regional Information (Application forms, administrative and prescribing information)

2) Summaries (Summarizing Modules 3, 4, and 5)

3) Quality

4) Safety

5) Efficacy

The guidances of direct interest to testing laboratories are the initial FDA guidance, plus M4—CTD Organization and M4S—Safety, covering the content and format of Module 2, sections 2.4 and 2.6, and Module 4. The guidance M4S covers the summaries in Module 2, which are of nonclinical data, as well as the organization of Module 4 itself. The instructions for Modules 2 and 4 are described in detail in the following section.

Nonclinical Summaries and Tables

The strict formatting of the CTD is well illustrated by the Table of Contents for each Module. This is the overall contents table for Module 2:

2.1 CTD Table of Contents

2.2 CTD Introduction

2.3 Quality Overall Summary

2.4 Nonclinical Overview

2.5 Clinical Overview

2.6 Nonclinical Written and Tabulated Summaries

2.7 Clinical Summary

The instructions for the preparation of section 2.4, the nonclinical overview, are fairly general and in line with the general requirements of 21CFR3 12.23 paragraph 8.

The Nonclinical Overview should be presented in the following sequence:

2.4. NONCLINICAL OVERVIEW

2.4.1 Overview of the Nonclinical Testing Strategy

2.4.2 Pharmacology

2.4.3 Pharmacokinetics

2.4.4 Toxicology

2.4.5 Integrated Overview and Conclusions

2.4.6 List of Literature Citations

Order of Presentation of Information within Sections

When available, in vitro studies should precede in vivo studies. Where multiple studies of the same type are summarized within the Pharmacokinetics and Toxicology sections, studies should be ordered by species, by route, and then by duration (shortest duration first).

The order should be:

Species	**Routes of Administration**
Mouse Rat Hamster Other rodent	The intended route for human use Oral Intravenous Intramuscular
Rabbit	Intraperitoneal

Dog	Subcutaneous
Nonhuman primate	Inhalation
Other nonrodent mammal	Topical
Nonmammals	Other

The instructions for the mandatory organization of section 2.6, however are much more detailed than those given in the CFR. It is important to note that the guidance does not specify which tests are to be performed. It only gives the format in which the tests that are performed are to be reported. Exhibit 5.2 shows the exact format to be used for the nonclinical written and tabulated summaries in section 2.6.

Exhibit 5.2 TOC of Section 2.6

2.6. Content of Nonclinical Written and Tabulated Summaries

- 2.6.1 Introduction
- 2.6.2 Pharmacology written summary
  - 2.6.2.1 Brief Summary
  - 2.6.2.2 Primary Pharmacodynamics
  - 2.6.2.3 Secondary Pharmacodynamics
  - 2.6.2.4 Safety Pharmacology
  - 2.6.2.5 Pharmacodynamic Drug Interactions
  - 2.6.2.6 Discussion and Conclusions
  - 2.6.2.7 Tables and Figures (see Appendix A)
- 2.6.3 Pharmacology Tabulated Summary (see Appendix B)
- 2.6.4 Pharmacokinetics Written Summary
  - 2.6.4.1 Brief Summary
  - 2.6.4.2 Methods of Analysis
  - 2.6.4.3 Absorption
  - 2.6.4.4 Distribution
  - 2.6.4.5 Metabolism (interspecies comparison)
  - 2.6.4.6 Excretion
  - 2.6.4.7 Pharmacokinetic Drug Interactions
  - 2.6.4.8 Other Pharmacokinetic Studies
  - 2.6.4.9 Discussion and Conclusions

2.6.4.10 Tables and Figures (see Appendix A)

2.6.5 Pharmacokinetics Tabulated Summary (see Appendix B)

2.6.6 Toxicology Written Summary

2.6.6.1 Brief Summary

2.6.6.2 Single-dose Toxicity

2.6.6.3 Repeat-dose Toxicity (including supportive toxicokinetic evaluation)

2.6.6.4 Genotoxicity

2.6.6.5 Carcinogenicity (including supportive toxicokinetics evaluations)

2.6.6.6 Reproductive and Developmental Toxicity (including range-finding studies and supportive toxicokinetics evaluations)

2.6.6.7 Local Tolerance

2.6.6.8 Other Toxicity Studies (if available)

2.6.6.9 Discussion and Conclusions

2.6.6.10 Tables and Figures (see Appendix A)

2.6.7 Toxicology Tabulated Summary (see Appendix B)

Source: International Conference of Harmonization (ICH).

Appendix A of the guidance contains examples of the tables and figures that can be incorporated into the Written Summaries. These illustrations are generally very similar to those used in standard scientific papers. Appendix B contains actual templates for the various tables to be used in the Tabulated Summaries. These templates must be used.

There are 50 pages of these in the 115-page guide, along with 40 typical examples, contained in Appendix C. Some examples of the tables in Appendix C are given in Exhibits 5.3 through 5.6.

Exhibit 5.3 Example of Pharmacology Summary Table

EXAMPLE

2.6.3.1 Pharmacology — Overview — Test Article: Curitol Sodium

Type of Study	Test System	Method of Administration	Testing Facility	Study Number	Location Vol.	Location Section
1.1 Primary Pharmacodynamics						
Antiviral activity vs. VZV	Human embryonic lung fibroblasts	In vitro	Sponsor Inc.	95401	1	
Antiviral activity vs. VZV	Clinical isolates	In vitro	Sponsor Inc.	95402	1	
Antiviral activity vs. HSV	Human embryonic lung fibroblasts	In vitro	Sponsor Inc.	95406	1	
Antiviral activity vs. CMV	Human embryonic lung fibroblasts	In vitro	Sponsor Inc.	95408	1	
Antiviral activity vs. VZV	ICR mice	Gavage	Sponsor Inc.	95411	1	
Antiviral activity vs. SVV	African Green monkeys	Nasogastric Intubation	Sponsor Inc.	95420	1	
Secondary Pharmacodynamics						
Antimicrobial activity	Gram-positive and gram-negative bacteria; yeasts	In vitro	Sponsor Inc.	95602	1	
Safety Pharmacology						
Effects on central nervous system[a]	Mice, rats, rabbits, and cats	Gavage	Sponsor Inc.	95703	2	
Effects on cardiovascular system	Dogs	Gavage, i.v.	Sponsor Inc.	95706	2	
Pharmacodynamic Drug Interactions						
Interactions with anti-HIV activity of AZT	Human T lymphocytes	In vitro	Sponsor Inc.	95425	2	

a – Report contains a GLP Compliance Statement

Source: International Conference of Harmonization (ICH).

Exhibit 5.4 Example of a Specific Pharmacokinetics Table

EXAMPLE

2.6.5.9 Pharmacokinetics: Metabolism *In Vivo* **Test Article:** Curitol Sodium

Gender (M/F) / Number of animals:	**Rats:** 4M	**Dogs:** 3F	**Humans:** 8M
Feeding condition: Fed			
Vehicle/Formulation:	**Rats:** Solution/water	**Dogs:** Capsules	**Humans:** 75-mg tablets
Method of Administration:	**Rats:** Gavage*	**Dogs:** Oral Capsule*	**Humans:** Oral Tablet
Dose (mg/kg):	**Rats:** 5 mg/kg	**Dogs:** 5 mg/kg	**Humans:** 75 mg

Radionuclide: ^{14}C

Specific Activity: 2 x 10^5 Bq/mg

Species	Sample	Sampling Time or Period	% of Dose in Sample	% of Compound in Sample: Parent	M1	M2	Study Number	Location in CTD: Vol.	Section
Rats	Plasma	0.5 hr	-	87.2	6.1	3.4	*95076*	26	
	Urine	0-24 hr	2.1	0.6	n.d.	0.2			
	Bile	0-4 hr	28.0	15.5	7.2	5.1			
	Feces	-	-	-	-	-			
Dogs	Plasma	0.5 hr	-	92.8	n.d.	7.2	95082	26	
	Urine	0-24 hr	6.6	6.4	n.d.	n.d.			
	Bile	0-4 hr	32.0	28.5	2.8	n.d.			
	Feces	-	-	-	-	-			
Humans	Plasma	1 hr	-	87.5	trace	12.5	CD-102	42	
	Urine	0-24 hr	5.5	2.4	2.9	n.d.			
	Bile	-	-	-	-	-			
	Feces	-	-	-	-	-			

Additional Information

* - Intraduodenal administration for collection of bile.
n.d. - None detected.

Source: International Conference of Harmonization (ICH).

Exhibit 5.5 Example of a Toxicology Summary Table

EXAMPLE

2.6.7.1 Toxicology — Overview — Test Article: Curitol Sodium

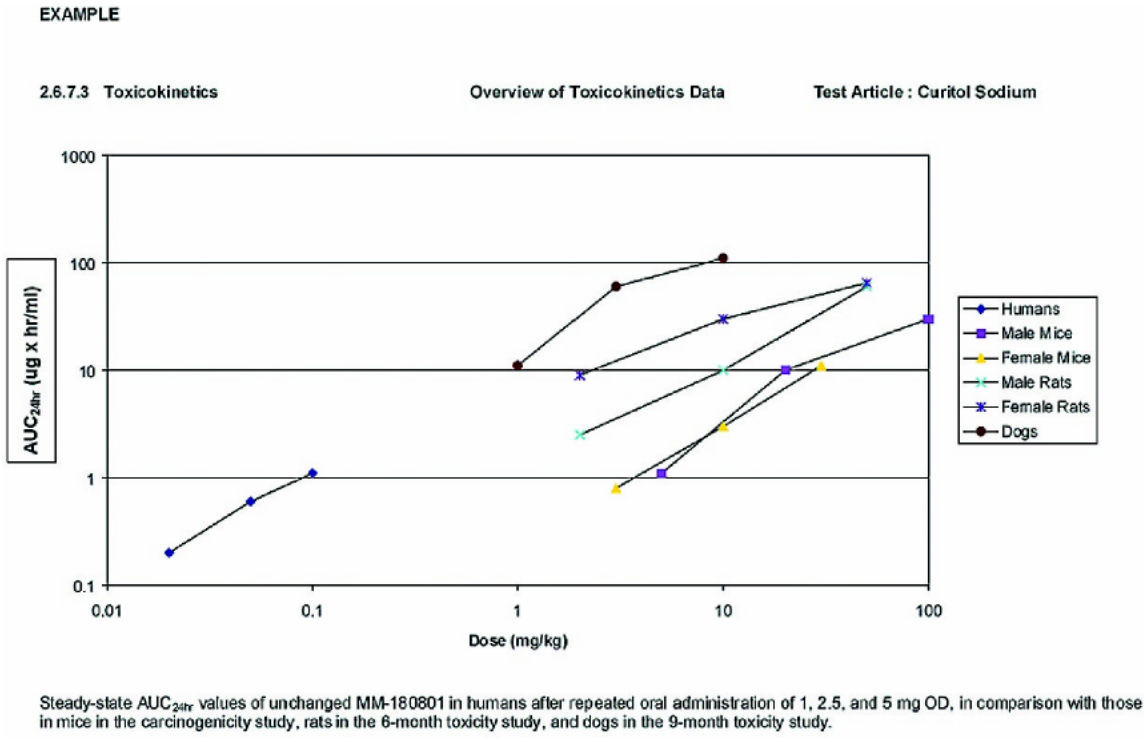
Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg[a])	GLP Compliance	Testing Facility	Study Number	Location Vol. Section
Single-Dose Toxicity	CD-1 Mice	Gavage	-	0, 1000, 2000, 5000	Yes	Sponsor Inc.	96046	1
		Intravenous	-	0, 100, 250, 500	Yes	CRO Co.	96047	1
	Wistar Rats	Gavage	-	0, 1000, 2000, 5000	Yes	Sponsor Inc.	96050	1
		Intravenous	-	0, 100, 250, 500	Yes	CRO Co.	96051	1
Repeat-Dose Toxicity	CD-1 Mice	Diet	3 Months	0, 62.5, 250, 1000, 4000, 7000	Yes	CRO Co.	94018	2
	Wistar Rats	Diet	2 Weeks	0, 1000, 2000, 4000	No	Sponsor Inc.	94019	3
		Gavage	2 Weeks	0, 500, 1000, 2000	No	Sponsor Inc.	94007	3
		Gavage	3 Months	0, 200, 600, 1800	Yes	Sponsor Inc.	94214	4
		Gavage	6 Months	0, 100, 300, 900	Yes	Sponsor Inc.	95001	5
	Beagle Dogs	Capsules	1 Month	0, 10, 40, 100	Yes	Sponsor Inc.	94020	6
		Capsules	9 Months	0, 5, 20, 50	Yes	Sponsor Inc.	96041	7
	Cynomolgus Monkeys	Gavage	5 Days	0, 500, 1000	No	CRO Co.	94008	8
Genotoxicity	S. typhimurium and E. coli	In Vitro	-	0, 500, 1000, 2500, and/or 5000 mcg/plate	Yes	Sponsor Inc.	95718	9
	Human Lymphocytes	In Vitro	-	0, 2.5, 5, 10, 20, and 40 mcg/ml	Yes	CRO Co.	97634	9
	Wistar Rats	Gavage	3 Days	0, 1000, 2000	Yes	Sponsor Inc.	95037	9

a - Unless otherwise specified. For Single-Dose Toxicity and Repeat-Dose Toxicity, the highest NOAEL (No Observed Adverse-Effect Level) is underlined.

(Continued)

Source: International Conference of Harmonization (ICH).

Exhibit 5.6 Example of a Toxicokinetics Summary Graph



Source: International Conference of Harmonization (ICH).

Module 4—Nonclinical Data

The format of section 2.6 is followed equally closely in the contents of Module 4, which contains the complete nonclinical data, principally in the form of Study Reports. This is shown in Exhibit 5.7. Note that section 4.2.2.1 requires the validation reports on the analytical methods used in the PK studies, if these are available. The first document in this module should be a table of contents listing all of the documents provided for module 4.

Exhibit 5.7 Table of Contents of Module 4

4.1 Table of Contents of Module 4

4.2 Study Reports. These should be presented in the following order:

- 4.2.1 Pharmacology
  - 4.2.1.1 Primary Pharmacodynamics
  - 4.2.1.2 Secondary Pharmacodynamics
  - 4.2.1.3 Safety Pharmacology
  - 4.2.1.4 Pharmacodynamic Drug Interactions
- 4.2.2 Pharmacokinetics
  - 4.2.2.1 Analytical Methods and Validation Reports (if separate reports are available)
  - 4.2.2.2 Absorption
  - 4.2.2.3 Distribution
  - 4.2.2.4 Metabolism
  - 4 2.2.5 Excretion
  - 4.2.2.6 Pharmacokinetic Drug Interactions (nonclinical)
  - 4.2.2.7 Other Pharmacokinetic Studies
- 4.2.3 Toxicology
  - 4.2.3.1 Single-Dose Toxicity (in order by species, by route)
  - 4.2.3.2 Repeat-Dose Toxicity (in order by species, by route, by duration; including supportive toxicokinetics evaluations)
  - 4.2.3.3 Genotoxicity
    - 4.2.3.3.1 In vitro
    - 4.2.3.3.2 In vivo (including supportive toxicokinetics evaluations)
  - 4.2.3.4 Carcinogenicity (including supportive toxicokinetics evaluations)
    - 4.2.3.4.1 Long-term studies (in order by species; including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
    - 4.2.3.4.2 Short- or medium-term studies (including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
    - 4.2.3.4.3 Other studies
  - 4.2.3.5 Reproductive and Developmental Toxicity (including range-finding studies and supportive toxicokinetics evaluations) (If modified study designs are used, the following sub-headings should be modified accordingly.)
    - 4.2.3.5.1 Fertility and early embryonic development
    - 4.2.3.5.2 Embryo-fetal development

4.2.3.5.3 Prenatal and postnatal development, including maternal function

4.2.3.5.4 Studies in which the offspring (juvenile animals) are dosed and/or further evaluated.

4.2.3.6 Local Tolerance

4.2.3.7 Other Toxicity Studies (if available)

4.2.3.7.1 Antigenicity

4.2.3.7.2 Immunotoxicity

4.2.3.7.3 Mechanistic studies (if not included elsewhere)

4.2.3.7.4 Dependence

4.2.3.7.5 Metabolites

4.2.3.7.6 Impurities

4.2.3.7.7 Other

4.3 Literature References

Source: International Conference of Harmonization (ICH).

Provided individual study reports are written according to the recommendations in 21CFR58, it is only their order of presentation that is controlled by the CTD recommendations for Module 4. A reminder that the content of Module 4 is not mandated—the sponsor must determine what tests should be performed in order to demonstrate the safety and lack of toxicity of the experimental drug. You should provide each study report and each related document as an individual document, separated from the other documents by binders or tab identifiers. Each literature reference should also be provided as an individual document, separated from the others by tab dividers.

The CTD format can be used for an amended submission, whether or not a previous submission was made in the old format. It is required, however, that formats should not be mixed. FDA requires that all documents should be bound in separate volumes, or smaller documents can be combined in volumes as long as they are separated by appropriately named tab identifiers. For example, the user fee cover sheet for a submission should be separated from the other documents by a tab identifier named user fee cover sheet. In general, documents from different CTD modules should not be included in the same volume. You may want to combine documents from different modules in the same volume for amendments consisting of a small number of short documents. Other general recommendations for the CTD documents will be found in the guidance *"Submitting Marketing Applications According to the ICH-CTD Format – General Considerations."*

It is recommended that, before preparing an IND, the regulatory authority should be contacted for a pre-IND meeting. At this meeting the proposal to use the CTD format can be discussed and comments sought on the proposed content, relevant to the clinical stage of drug development.

CHAPTER 6: GLP INSPECTIONS AND STUDY AUDITS

What Are Inspections and Audits?

The regulations considered in Chapters 3 and 4 all require that the GLP compliance of the operations of a facility, and any study performed therein, must be confirmed by an independent inspection of the facility and by audits of the study data. These actions are carried out by specialist staff of the national regulatory agency or, occasionally, by consultants hired by the agency to perform a specific inspection or audit. The FDA and OECD have published Guidelines for such inspections and audits and for the preparation of reports on these activities. In the United States, inspections are now performed under the FDA's Office of Regulatory Affairs (ORA) Bioresearch Monitoring (BIMO) Program. This program is handling the GLP surveillance of nonclinical testing laboratories and the compliance with Good Clinical Practice of clinical investigators, clinical trial sponsors/monitors and institutional review boards (IRB). Guidelines for BIMO inspections were issued in February 2001. The section III, dealing with procedures, is reproduced in Chapter 9.

Establishment Inspections

An initial inspection is always performed when a new facility first files a study claiming to be GLP compliant, and facilities must be re-inspected about every two years (FDA recommendation) in order to maintain their GLP recognition or registration. All inspections of commercial laboratories are conducted without prior notification, unless the FDA Field Center involved decides otherwise. However, the inspectors must notify a university or government laboratory by letter when an initial inspection is to be performed. Subsequent inspections may be made without notice.

FDA specifies two types of inspection:

1) Surveillance Inspections, which are the periodic, routine determinations of a laboratory's GLP compliance, inspecting the facilities and auditing studies in progress and/or studies recently completed. The inspectors' assignments may identify one or more specific studies to be audited. If the assignment does not identify a study for coverage, or if the referenced study is not suitable to assess all portions of current GLP compliance, FDA recommends that the investigator should select studies as necessary to evaluate all areas of laboratory operations. When additional studies are selected, first priority will be given to FDA studies for submission to the assigning Center (CDER, CBER, CDRH). It is noted that studies performed for submission to other government agencies, such as Environmental Protection Agency, National Toxicology Program, and National Cancer Institute, should not be audited without authorization from the Bioresearch Monitoring Program Coordinator. However, this authorization is not necessary for the inspectors to look briefly at one of

these studies to assess the ongoing operations of a portion of the facility.

2) Directed Inspections, which are assigned by the FDA Centers to achieve a specific purpose such as verifying the integrity and reliability of a specific critical study currently under review or investigating issues involving potentially unreliable safety data or violations brought to FDA's attention by FDA reviewers or outside sources, often termed "whistle-blowers." Directed inspections may also be scheduled to confirm that a facility has corrected previously notified violations or non-compliant practices or to verify the results from third-party audits or sponsor audits submitted to FDA for consideration in determining whether to accept or reject questionable or suspect studies.

The team of inspectors will include a field investigator as Team Leader, familiar with the performance of visits to facilities and technical support will be provided by field analysts and perhaps specialist staff from FDA headquarters. Sometimes other agencies, such as the Environmental Protection Agency may also send observers, but FDA staff will be in charge of the operation.

The performance of a surveillance inspection is described by the FDA Guideline as follows: "The investigating team will determine the current state of GLP compliance by evaluating the laboratory facilities, operations and study performance."

The Master Schedule for all studies listed since the last inspection will be accessed. For an initial inspection the entire Master Schedule is examined. Ongoing and completed studies are selected for examination on the basis of these criteria:

- Safety studies conducted on FDA-regulated products that have been initiated or completed since the last inspection, or
- Safety studies that encompass the full scope of laboratory operations, or
- Studies that are significant to safety assessment, e.g., carcinogenicity, reproduction or chronic toxicity studies, or
- Studies that encompass operations with several animal species.

For ongoing studies, a copy of the protocol is examined and the schedule of activities is determined. The inspectors will then be able to schedule inspection of various facility areas when they are in use and activities relating to the study as they are happening. For completed studies, a ***data audit*** is performed, as detailed in the following section.

FDA staff are instructed to be guided by the GLP regulations in the performance of the facility inspection. I have produced a set of forms, shown in Appendix 9.1, that demonstrate the means whereby this operation can be performed. If one follows the set of forms through, it can be seen that each section of the regulations is dealt with in turn and comments can be made on any

activity that seems to be non-compliant. The inspectors are entitled to request a copy of any document relating to the operation of the facility or to the study under inspection, including CVs, protocols, SOPs, study reports, and QA reports. They may also take specimens for examination and take photographs for inclusion in their report. They may interview any staff involved in the running of the establishment or conduct of the study. Explanations of certain activities or for observed discrepancies may be requested from facility staff at the time, but it is typical for all discrepancies to be listed at the end of the inspection and discussed at the closing meeting with the facility staff.

Key Inspection Points

Although all sections of the GLP regulations must be followed, the inspectors are instructed to pay particular attention to the following points. These are listed in some detail here, as a guide to those areas where the inspectors are accustomed to finding non-compliance, or where they consider it is particularly important to check compliance:

- Determine the areas of expertise in use at the facility (i.e., types of studies performed).
- Check that the organizational structure is appropriate; all staff must be fulfilling their responsibilities—look for evidence of management involvement in mandated areas, (e.g., appointment of SD and QAU, provision of GLP training, characterization of samples).
- Review personnel records for summaries of training and job descriptions. Check that personnel show observance of correct health precautions, wear appropriate clothing.
- Determine who was involved in design, development, and validation of any computer system and who is responsible for its operation—have computer staff been adequately trained? (N.B. There is a separate Attachment A to the Inspection Manual which covers computer inspections. This will also be found in Chapter 9, and should be read in conjunction with the new 21CFR1 1 Guidance, issued in 2003.)
- Interview and observe key study personnel to assess training and performance of assigned duties.
- Study Director: assess extent of SD's direct involvement and participation in the study. Review SD procedures for protocol administration, data collection, study records, and documentation of unforeseen occurrences.
- QAU: determine that the QAU is effective, independent, and monitors significant study events. Review QAU SOPs for all QA functions.
- Facilities: review design and space allocation, environmental control and monitoring for critical areas, cleaning/maintenance SOPs.
- Equipment: determine whether equipment is maintained and operated in a manner that

ensures valid results. Note that this will include the heating, ventilation, and air conditioning systems for the facility and any special provisions for isolation or biohazard containment. SOPs, operating manuals, and maintenance logs should be inspected.

- Facility Operations: All SOPs will be reviewed for this function. Verify that only current SOPs are in use. Check maintenance of historical files for SOPs and especially for computer programs.
- Reagents & Solutions: Check that the facility ensures the quality of these on receipt. Review purchasing, receiving, labeling, and storage procedures.
- Animal Care: Care and housing must be adequate to preclude stress and uncontrolled influences that could alter test system responses. The animal rooms must be inspected to observe SOP adherence and the maintenance of adequate records. Determine whether the facility has an Institutional Animal Care and Use Committee. If so, obtain copies of the Committee's SOPs and the most recent committee minutes to verify committee operation.
- Test & Control Articles: accountability for these must be maintained. Adequate procedures for their handling must be in place. If possible, observe the preparation, sampling, testing, storage, and administration of carrier mixtures, if used. Confirm that adequate characterization of test articles has been performed. Check correct identification of all test/control articles throughout the facility and reconciliation of quantities in completed studies.
- Protocol & Study Conduct: Determine whether the protocols are properly written and correctly observed during the conduct of the study. Review all changes, revisions, and amendments to ensure proper authorization and signatures. In study conduct, animals must be correctly randomized according to SOP.
- Recording of Data: Confirm that entry corrections do not obscure original entries and that access to computer data entry and alteration is restricted and recorded.
- Records & Reports: Examine the facility's ability to store and retrieve data, reports, and specimens so as to preserve their integrity and utility.
- Final Report: This must contain the dated signature of SD, descriptions of computer program changes, and clear identification of any amendments to the original report.

Study Audits

In addition to the general evaluation of the facility and the conduct of studies, the inspectors are instructed to perform at least one audit of a completed study. This will involve a detailed comparison of the protocol and its amendments, raw data, records, and specimens against the final report. The purpose of the audit will be to confirm that the protocol requirements were met and that the findings were fully and accurately reported.

Particular attention is paid by the inspectors to the following factors:

- General:
  - Quality of the records; legibility, ink, signing, correct alterations or amendments. All raw data documents must be attributable and traceable to the person observing and entering the data.
  - Any significant changes in facility operations, QAU function, and whether these were correctly recorded.
  - Equipment calibration, standardization, calibration, maintenance & correction of malfunction.
  - SOPs: did approved versions of these exist during the study?
  - Protocol: compliance with 21CFR58 requirements.
  - SD signature and QA signed statement in final report.
- Protocol vs. Final Report. Study methods described in the protocol must have been followed and the final report should show this for:
  - The test systems;
  - For animal tests: receipt, quarantine of animals;
  - Methods of test system identification;
  - Any diseases occurring and treatments;
  - Validation of suitability of feed and bedding;
  - Preparation and administration of test and/or control articles and analysis of article/carrier mixtures;
  - Observation of response of the test system to the article under study;
  - Collection and analysis of specimens and data; and
  - Necropsy and histopathology.
- Final report vs. Raw Data. This is the most critical area of the audit. It must confirm that the findings in the final report are substantiated by the raw data and completely and accurately reflect the raw data. The instructions to inspectors give examples of the type of data to be checked. It is not necessary to give an exhaustive list here, but the following have been highlighted as sources of error or omission:
  - Records of the analysis, characterization, and stability testing of test and control materials;
  - Animal weight gain and food consumption records;
  - Consistency of animal/specimen identification, to be checked by a random, complete "paper trail" trace from receipt of the animal to examination of histopathology specimens;
  - Data consistency (i.e., within one dosage level) there should be an acceptable range

of documented responses, with upper and lower limits of acceptable levels established and explanations given for data outliers;

- Correlation between in vivo observations and gross pathology;
- Correlation between reported "interim" values and "final" values; and
- Inspectors should do a random check of retained specimens in the archives, to confirm the number and identity of retained specimens reported in the final report.

Establishment Inspection Report (EIR)

This is the official title of the report that will be made to the FDA following the inspection. A report of an initial inspection must be in full format, covering all the details given above. Later directed inspections and specific data audits may be reported in a more abbreviated form. All reports will contain the following information:

- Full name, title, academic degrees and mailing address of the most responsible person. For universities, this individual would typically be a member of the administration (e.g., department head, dean, etc.);
- Summary of findings;
- Description of any significant changes in laboratory management or operations since the last inspection;
- Identity of the studies selected for audit;
- Identification of areas, operations and amount of data inspected (e.g., identity and percent of records reviewed in a specific area, number of animals tracked, percent of slides checked for accountability, etc.);
- Full discussions of all adverse observations, with documentation to permit assessment of their effect on the quality and integrity of the study; and
- The full report will, in addition, contain details on all Key Inspection Points and the Study Audit Factors listed above.

In areas where no deficiencies were found, the operations inspected must be identified but need not be described in detail. Where discrepancies are described, the responsible Center must determine the content of any post-inspection correspondence to be sent to the facility's responsible person. Serious deviations from GLP, which might have compromised the validity of any study, will be notified on FDA Form # 483, which will require immediate corrective action to be undertaken by the facility, or which might disqualify a testing facility or a specific study.

Deviations which are not required to be notified by FDA 483 are:

- Deviations that have been observed and corrected by the laboratory through its internal

audit procedures; and

- Minor, one-time occurrences that have no impact on the laboratory's operations and/or study conduct.

Findings not considered significant enough to be listed on the FDA 483 may be discussed, along with the Form 483 comments, with the facility management at the immediate wrap-up meeting. Such discussions must be reported in the EIR. Since the issue of a FDA 483 constitutes a legal notice, inspectors are required to collect, submit, and reference in the EIR sufficient documentation to support the information in FDA 483 and this documentation may form the basis for legal or administrative action under CFR2 1.

The issue of FDA 483, or any equivalent document by another national authority, may be followed up by additional special inspections, to confirm that the required corrective action has taken place. If additional data are required in order to qualify a particular study, these will be audited. If all goes well, the facility will eventually receive confirmation that it is again in GLP compliance and will be allowed to submit new studies in the future.

How to Survive Inspections and Audits

Only one word is needed to describe the method by which inspections and audits can be satisfactorily survived: **PREPARATION**. The inspection process falls into three stages—before, during and after—and all three of these can be prepared for. We will consider them in order.

Before—Preparing for the Inspection

Only university and government laboratories will have proper notice of an inspection. In the case of commercial laboratories, some notice may be given, but unannounced visits are also permitted. This means that once the facility has been responsible for a study that has been submitted to the agency, it must be in an adequate state of preparedness to survive the coming inspection. Remember, there are also inspections performed approximately every two years of facilities that have been in operation for some time. to the next sections will list some very obvious preparative activities, but it is surprising how many times the imminence of a FDA inspection causes lapses in logical thinking and common sense. The activities fall under three categories: the place, the people, and the paper.

- The Place: This is where it's going to happen!
  - Management should perform a thorough walk-through of the entire facility and look for any areas needing refurbishing, any equipment needing cleaning or repair, and a general tidy-up should be performed if necessary. The inspectors will know that this is often a last-minute activity and will not be surprised to smell fresh paint,

but at least it will have been done.

- Unused or surplus equipment should be removed from operating areas and stored. The less clutter the better.
- Check that all static pipework and equipment is properly labeled and reagent labels are GLP-compliant.
- Pay particular attention to the warehouse and sample storage areas.

- The People: You can't do it without the staff.
  - First, designate the person who will be responsible for escorting the inspectors through the facility and answering general questions about operations. This person is usually the QA manager, or perhaps the Study Director. This representative should have the authority to speak for the facility management and be knowledgeable about the studies. Have a back-up person identified to cover absences.
  - Other persons will be required to answer particular questions or demonstrate particular activities, but one very good piece of advice is to restrict the number of people who will be touring with the inspector(s) to a minimum. The sight of a large group of managers trying not to look worried as they accompany a couple of inspectors, who are trying to get as much information about the facility and operations in as short a time as is feasible, sometimes verges on the farcical. It is certainly counter-productive.
  - Make a list of key people who may be required to address study topics. See that these people have an outline of their areas of responsibility and check for gaps or overlaps. Again, see that they are backed up by substitutes.
  - The "tour coordinator," as we may call him/her, should perform a mock inspection, along with the QA unit, a day or two before the FDA visit, if notified, and familiarize themselves with potential problem areas. If notice is not expected, arrange for regular mock inspections as part of the QA function.
  - Don't forget that the plant manager will also be needed to answer questions about HVAC and other systems.
  - All staff members should be briefed to the effect that they may be questioned at any time, especially about an operation they are performing at the time of the inspection, or about something for which they are routinely responsible, such as autoclave operation.
  - It is important that they are told: "Do not panic. Be sure you understand the question, if not, ask for clarification. Then: answer the question you are asked to the best of your ability. If you do not know the answer, say so and refer to a colleague, supervisor, or senior who may be able to answer.
  - Don't guess or invent and don't volunteer unasked-for information. It is also

unadvisable to play "word games" with inspectors, in an attempt to side-track the inquiry. It is much better to admit you don't know the answer, or that you will need time to sort out the details, and say 'I'll have to get back to you on that." Then you should make certain that you do.

- Inspectors are instructed not to be threatening or overbearing in their behavior. If you feel threatened by a question, try to defuse the situation by rewording it so that it seems more neutral to you. If asked "Why did you do this ...?" You may say "Do you mean why do we have an SOP that instructs us to do that...?" (i.e., what is the company policy...?).
- Staff should know where essential equipment and SOPs are located. If they are actually performing an operation of any sort, they should ensure that the SOP is clearly available—not in a drawer, also any equipment operating manuals that are referred to in the SOP.
- All staff likely to be met by the inspectors should wear name badges on inspection days. Have these ready.
- See that offices or writing areas that may be visited are clean and tidy and that any documents or computer screens exposed are suitable for inspectors to see.

- The Paper: Documentation is all-important.
  - Start with the plan of the facility and detailed plans of all the services, especially HVAC. Remember the aim here is to show that there is adequate separate space allocated for the various operations and adequate separation of air systems and operating areas to prevent cross-contamination. Special specifications for walls and floors to ease cleaning and sanitization should also be documented.
  - If tests have been performed to demonstrate the correct air flows in the building, then the test documents should be available for review.
  - Where incubators, sterile areas, and such are continually monitored, records from the temperature recorders, plenum gauges, etc. must be available. Be sure recorder charts are changed at the proper times.
  - Provide a full staff list with qualifications and short position descriptions. Ensure that staff records that detail evaluations and training, especially GLP, are available for review if needed.
  - Ensure the SOP file is up-to-date and all operating areas have the current version of the SOPs they need. Don't forget those written for the building cleaning and maintenance, which should be in the plant office. Management is often surprised that the inspectors will "bother themselves about such a minor matter." If absence of these shows that management is not doing a good job, then it's not a minor matter.
  - Have the laboratory records books for all ongoing studies available and be able to

access rapidly any final report and raw data or specimen archives requested for any completed study. Usually, the inspector will go through the Master Schedule and indicate which ongoing study will be inspected and which completed study will be audited, so that the staff will have time to have the documents retrieved.

Since commercial organizations will not have the benefit of a warning that an inspection is to take place, it is incumbent upon management to have the preparatory work described above done fairly soon after a submission has been made to the regulatory authorities for the filing of the first GLP study in a new facility. The submission will trigger the initial inspection, and subsequent inspections will occur approximately every two years after that. Since the actual dates will be unknown, management is well advised to ensure regular updates in the preparatory operations. After all, a facility that is being properly run according to GLP and to the recommendations in this book should be prepared for an inspection at any time. Writing an SOP to cover this type of inspection preparation is probably an advisable activity.

During—Inspection Days

If the preparatory work has been well done, the actual inspection will run very smoothly and it will only be necessary to ensure that certain physical arrangements are made.

- Ensure that reception staff knows how to handle the appearance of the inspectors in the entrance hall.
- Reserve a suitably sized conference room for the first and last meetings and arrange for a quiet room where the inspectors can work alone, to review documents and write up their findings. See it has plenty of table space for documents and perhaps a copier. Although I consider it more appropriate for copies to be made by laboratory staff on request (see below). Make adequate provision for food, drink, and preferably private restroom facilities, without going to unnecessary and potentially embarrassing lengths.
- Inspectors are not allowed to accept any form of hospitality beyond that normally available to staff members. They should eat alone, or in the executive dining room, if there is one, so that there is some measure of privacy and a chance to meet more of the senior staff, but the meal should not be specially catered. Do not arrange to take them by limousine to a nearby fancy restaurant for lunch or dinner and do not offer transportation beyond offering to collect them from their hotel and return, if they have come from out of town.
- Ensure the inspectors have adequate time to look at operations and facilities and discuss points with the operating staff. Set aside some time on the first day on arrival for discussion of the inspection schedule and adequate time on the last day for the "wrap-up" session.

- Do not disrupt the normal schedule of the facility, beyond ensuring the availability of key staff. The inspectors will want to see the laboratories running, not shut down and cleaned up. See that people have relatively clean lab coats (not brand new ones!) and are wearing their name badges.
- Provide appropriate protective clothing for the inspectors where this would normally be worn. Make certain the inspectors follow all safety codes.
- Do not be surprised if the inspectors spend what seems to be a disproportionate amount of time on the QA unit. Remember, the performance of the QAU will reflect management's commitment to overall compliance. The SOPs for QAU operations will be specially scrutinized. The better the job that the QAU is doing, and the better it seems to the FDA personnel, the more likely it is that the inspectors will accept the facility operations and test data as being satisfactory.
- Provide an assistant to collect all documentation that the inspectors wish to have copied and ensure that the copies are available by the end of the working day, properly collated and indexed. This is easier and safer than having the inspectors try to do it themselves. At the same time, a list of the documents supplied can be made and finally receipted by the inspectors before they leave. Some companies make two copies of each requested document, provide one to the inspectors and keep one copy for the in-house inspection file.
- Responses to queries should be quick and accurate, where at all possible. Rapid access to documentation is often the answer, especially to deal with questions about deviations from the protocol, etc.
- If specimens or samples are requested to be removed by the inspectors, ensure that this will not deplete the reserves beyond workable levels. If this is likely, discuss the situation with the inspectors and arrive at some reasonable compromise. Mark the specimen or sample records to reflect any removals for inspection purposes. Get a receipt from the inspectors.
- A simple request form, as shown in Exhibit 6.1, can serve to ensure that all requests are properly handled.

Exhibit 6.1 Inspection Request Form

INSPECTION REQUEST ACTION FORM
Date:
Inspector Name/ID#:
Subject:
Requests:
1.
Completed ☐
2.
Completed ☐
3.
Completed ☐
Print Name:
Signature:
(Note: Check box as each item is completed)

Source: D&MD Publications.

After—Dealing with the Report

The wrap-up meeting provides an opportunity for immediate answers to be given to some of the inspectors' questions and for the facility staff to get immediate information on the Form 483 contents. It is not a meeting at which the staff should argue with the inspectors or with each other—rational discussion is one thing, but accusations of prejudice, complaints, or recriminations have no place here. The staff can and should respond to the FDA 483 comments during the discussion with the inspectors. If there are questions on scientific or technical matters that need to be clarified, this should be done.

If the laboratory disputes any observation, it is essential that both the inspectors and the laboratory staff understand exactly what the issue is, so that it can be properly discussed and a resolution achieved. It is very important for the laboratory staff to display a cooperative and

proactive attitude.

In fact, corrective actions or procedural changes that are accomplished or at least initiated in the presence of the inspectors are regarded as positive indications of your concern and desire to correct discrepancies voluntarily. Thus, when potentially serious non-compliance issues have been raised, the best approach is to initiate immediately a complete investigation of the reasons for the violation and a rapid correction of the problem. If, for any reason, a dispute over the observations of the FDA inspector has not been resolved at the wrap-up meeting, or the lab staff are confused about what actions should be taken, you should contact the Director of Investigations Branch in the relevant FDA Field Center to resolve your concerns. Or, you may be referred to the relevant Agency Center (CDER, CBER, CDRH).

Once the formal correspondence has been received from the Field Center, the facility's official written response should be able to show that some effort has already been made along these lines. If an in-house investigation has already yielded results, then these can be described. If corrective action has resolved the problem, so much the better, and the results of recalibration of the equipment, re-validation of the test methods, or other changes, can be included in the response. If a certain test result will be available at a known date, then say so and ensure that the results are communicated to the Center as soon as they are available.

It is very rare for a GLP facility actually to be disqualified after an inspection. Usually, the management is given ample opportunity to correct violations and a second inspection confirming compliance may complete the procedure. At most, some tests may have to be repeated. It is essential, therefore, to respond rapidly and positively to any adverse comments made by the inspectors and to ensure that they will not find the same errors next time. If the responses are considered to be unsatisfactory, or if the relevant FDA Center considers that the violations cited in the Form 483 are serious enough, a Warning Letter may be issued to the Chief Executive of the company. This will require certain activities to be performed within 15 working days of receipt of the letter. The contents of warning letters are published on the FDA's Web site, along with companies' responses. These documents can harm a company's reputation—in addition, if the letter is not fully complied with, further legal action may follow rapidly.

How Others Fared—Excerpts from Form 483

The Freedom of Information Act has meant that, subject to the removal of proprietary information from the documents, the contents of actual Form 483 reports can be reviewed by the public. Here are some typical excerpts, to demonstrate the type of concerns inspectors may develop during an inspection, and the extent of their detailed analysis of procedures and processes. In some cases I have added italics for emphasis. Any comments I have made are given outside the quotation marks.

- "During validation of the laboratory computer system at installation, only calculations producing results within expected ranges were verified versus manual calculations. No testing was done of other conditions, such as the entry of results at or outside expected limit ranges or inappropriate data entry. There were no written specifications for allowable variations in calculation checks."
- "In the method validation study for precision, the firm did not determine if the chromatographic system was stable within the concentration range of the samples. System suitability was determined from samples with a peak response approximately eight times higher than that of the standard." Not an acceptable practice.
- On the operation of a microhematocrit centrifuge: "The spin time for the microhematocrit centrifuge was based on a single test for [the] minimum time to achieve maximum packing. A microhematocrit centrifuge spin time of five minutes was used, although the test demonstrated the minimum time for maximum packing to be four minutes. Timer settings actually used are not recorded as part of the quality control or use records. The 1996 SOP for the microhematocrit centrifuge did not require recording actual times for timer verification and actual speed for RPM checks. The subsequent 1997 SOP does not require recording of actual speed for RPM checks."
- "The analyst was measuring the temperature of the water bath while holding the thermometer near the middle of the mercury column. This practice could cause erroneously high temperature readings due to body heat". It's the little things that can throw us.
- "Calibrated timing devices were not used when performing dissolution testing."
- "The filters used for filtering dissolved samples have not been checked for adsorptive loss of drug. The potential for cross-contamination of samples was incurred since the same filter was used to filter all samples within a run. The test procedure does not state that the first 5-ml of sample filtrate should be discarded. This practice leads to potential interference in the UV spectra." Sheer bad technique.
- "Tests performed on the UV spectrophotometer were not done at the UV maximum as specified in the SOP, but at one pre-set wavelength without a scan." A clear example of misuse of equipment.
- "Archives for studies performed in 1993 or 1994 are not secure, in that there was no limited access or check-in/check-out procedures observed when study records were removed. The SOP also did not address archive security or access by unauthorized personnel."
- "One page of the check-out log for archive materials showed that nine sets of materials were logged out since 199 1/92; these items were actually in the archives." The explanation was that the inspector was not shown subsequent pages of the log where the

return of the materials was recorded. The archivist should have picked this one up at the time.

- "Seventeen vials and two jars of wet specimens located in the annex to the necropsy room were not labeled". An ex-FDA consultant remarked in one published article that inspectors like to look at every label of every container they can see. Think of the opportunities for error that may occur with unlabelled necropsy samples!

The following are abstracts from recent warning letters, issued after the responses to the Form 483 observations were not considered to be satisfactory.

- "The Study Director has not noted unforeseen circumstances or deviations that may affect the quality and integrity of nonclinical studies when they occurred, and failed to document what corrective actions, if any, were taken at that time.
  - In several cases, deviations that occurred in studies 98-33, 98-54, and 98-63 were noted six months to more than one year later.
  - Several deficiencies were not documented until the time of the FDA inspection.

For example,

  - There are no records to support the conclusion represented in Amendment #005 to study 98-63.
  - Study personnel did not follow the protocol when changes were reportedly made to study 98-63.
  - Protocol section 'VII. Alteration of Design" states the following: "Alterations of this protocol may be made as the study progresses." It was inappropriate for the Study Director to prepare this protocol amendment one year after the study ended in the absence of supporting documentation. "

- "The QAU monitoring inspections failed to detect, resolve, or document deficiencies in the three studies reviewed during the Inspection, Many of the deficiencies noted below were not identified until the time of this FDA inspection. Examples of the QAU deficiencies include, but are not limited to, the following:
  - Some animals used in studies 01-23 and 01-24 did not meet the protocol-specified weight ranges, as described in item 8, below. There is no evidence that the QAU detected this protocol violation.
  - Study 01-24, animals #1593, #1594, and #1601 were reported as "found dead" by the study pathologist, but the necropsy and clinical pathology records indicate that these mice were sacrificed as scheduled. Please submit copies of the daily observation logs and cage cards for these animals.
  - The necropsy records for study 0 1-25 indicate that all tissues were taken and preserved at the time of necropsy however, the pathology report indicates that several key tissues (i.e., pancreas) were missing."

"Dr. W. (Study Director) signed protocol amendments #001 and ##002for study 98- 33 in the signature block for Study Sponsor even though he was not the sponsor of the study. There is no record that the sponsor signed these protocol amendments. The protocol states 'No changes in the protocol will be made without the consent of the Study Director and Study Sponsor. In the event that the Study Director must implement a protocol change, such changes will have written authorization. All protocol modifications will be signed by the Study Director and Study Sponsor'."

"There was no signature block for Study Sponsor signature for protocol amendment #010 for study 98-33. This protocol amendment changed the contractor originally selected to perform the histological evaluations for the study. The protocol amendment notes that the new contracting laboratory 'is not fully GLP compliant'."

"The testing facility management failed to designate a study director with the appropriate combination of education, training and experience necessary to oversee a GLP study and to carry out the responsibilities that are required under section 58-33. For example, the FDA inspection revealed that the study director failed to assure that the protocol, including any change, is approved (FDA-483, Item 4); that experimental data are accurately recorded and verified (FDA-483, Items 3,8 and 17); that applicable GLP regulations are followed (FDA-483, Items 1-18); and that raw data, documentation, protocols, specimens, and final reports are transferred to the archives during or at the close of the study (FDA-483, Items 7, 17-18)."

Of course, this is only a small example of the types of comments that may be found in the Form 483 reports or subsequent warning letters, but it should suffice to drive home the point—all of these citations could have been avoided without very much effort by correct adherence to GLP principles and with some care in the SOP writing and observance. In fact, the survival of FDA inspections and audits is not a difficult task. As I stated at the beginning of this chapter, "preparation is all", and before "preparation" for an inspection comes correct compliance procedures. It is incumbent upon everyone working in a GLP facility to be aware at all times of their need to follow absolutely the guidance of the SOPs and a routine of working which prevents avoidable errors and citations.

CHAPTER 7: CONCLUSIONS

After the analyses and recommendations that have occupied the first six chapters of this Guide, it is important to draw some conclusions which will enable the reader to hold the way to GLP compliance firmly in his or her mind. It would be easy just to say "You must follow every word that is written slavishly," but more is expected in this Guide than that bald statement.

So, a few conclusions to this Guide are:

- The key to achieving GLP compliance is the attitude of those in charge. If they are not convinced of the necessity to follow these guidelines, the task will fail. Ensure that management "runs a tight ship."
- The simplest way to have the staff comply is to write brief, easily understood but unequivocal SOP documents and ensure that they read and observe them. I remember reading a quotation in the Guide to Authors of the Journal of General Microbiology which stated "Easy writing is cursed hard reading; Easy reading is cursed hard writing". This holds true here, but the hard writing is well worth the effort.
- Ensure study protocol instructions are understood by all and that the SD makes sure that everyone follows them.
- Be meticulous with your labeling of samples, animals, and specimens.
- The QA unit is the conscience of the facility and one should "always let your conscience be your guide"... Pinocchio, was it? Remember, inspectors will look very closely at the way management supports the QAU and how well QA does the job.
- FDA's unwritten motto is "If it is not written down, it did not occur, or it does not exist". Your records are the only proof that you have done the job properly. Write well-defined protocols, and keep clear and exact records of each part of the study.
- Pay attention to the style and content of the Final Report. The Agency bases its assessment of the work primarily on this document.
- Preserve your archives as you would your reputation.
- Be certain to keep your knowledge of the relevant regulations up to date. The Guidances issued by FDA and OECD are invaluable indications of the way the Agencies are thinking.
- Don't neglect the need to keep everyone's training current, even the Chief Executive. Ensure you use a trainer with experience and an approach that all can respect. Make sure everyone's training records are complete.
- And finally, doing things right the first time is always less expensive than repeating studies or recovering from Form 483 or Warning Letter citations.

CHAPTER 8: REFERENCES AND FURTHER READING

Access to Regulatory Documents

Most regulatory authorities have a publications office from which their current documents can be obtained. With the enormous expansion of the Internet, however, the quickest and cheapest way to access these is through the following web pages:

- FDA*: www.fda.gov/cder* is the home site for the Center for Drug Evaluation & Research or /cber for biologics and /cdrh for devices. Once you reach any of these sites, /guidance will enable access to guidelines and other useful documents. The guidelines from the Office of Regulatory Affairs for bioresearch monitoring, which are intended for use by FDA inspectors, can be found at *www.fda.gov/ora/ compliance*.
- The Code of Federal regulations is accessed through the Government Publications Office, at *www.gpoaccess.gov/cfr/index*
- The OECD is accessed at www.oecd.org. Most of the GLP documentation is found at the site dealing with environmental matters. On the home page, click "Browse by Topic", then "Environment", then "Chemical Safety", then "Good Laboratory Practice". The "Publications" button will bring you to the actual guidelines.
- The European Agency for the Evaluation of Medicinal Products, EMEA, is the central office for submissions review for the entire community. It is part of EUDRA – European Union Drug Regulatory Authorities. The European regulations are found in EUDRALEX "The Rules Governing Medical Products in the European Union". The web site is *http://ec.europea.eu/enterprise/pharmaceuticals/eudralex*.
- Japan. The most useful site I have found for information on Japanese regulations is that of the Japan Society of Quality Assurance, at www.jsqa.com/en. This publishes "unofficial" translations of important regulatory documents in English, and they have the 1997 versions of the OECD Principles, as used in Japan on their site. Do not confuse this organization with the Japanese Society for Quality Control.
- Canada's Directorates for pharmaceuticals and biologicals regulation are accessed through Health Canada's Web site *www.hc-sh.gc.ca*

Useful Publications

Several US publications are continuing good sources of news and advice on regulatory matters. Prime amongst these are the monthly journal from Informa Healthcare – *The Regulatory Affairs Journal Pharma (RAJ Pharma)* and two from Advanstar Communications, *BioPHARM International and Pharmaceutical Technology*, all of which have regular regulatory columns. (The latter usually cover GMP matters, but also occasionally GLP.) In any event, the advice is always good. Subscription to the first is on a paid for basis; the other two are free for US residents – one simply fills in a questionnaire and sends off the postcard, or you can do it on-line, through their web sites, *www.pjbpubs.comraj_pharma*, *www.biopharminternational.com/biopharm* or *www.pharmtech.com*. Outside the US, one may have to pay postage.

Other trade journals with regular regulatory columns include *Contract Pharma* (*www.contractpharma.com*) and *Pharmaceutical Formulation & Quality – PFQ* (*www.pharmaquality.com*. These are also free in the US and Canada.

A useful online magazine for regulatory compliance news and information is *LabCompliance*, at *www.labcompliance.com*. This is run by Dr. Ludwig Huber, chief compliance officer for Agilent Corp., so it is a really helpful source. Much of the information Dr. Huber supplies is free. You can also subscribe to the club to get further data, buy his books, guidelines and SOPs, or visit his on-site seminars, which are particularly directed towards GLP compliance and GMP compliance in analytical laboratories. He is especially good on 21CFR11 problems.

The Regulatory Affairs Professionals Society, at *www.raps.org*, publishes the *Regulatory Affairs Focus* magazine and The Institute of Validation Technology publishes the *Journal of Validation Technology and the Journal of GxP Compliance*. Their Web site is *www.ivthome.com*

FDC Reports publishes several well-known weekly newsletters, especially "*The Pink Sheet*" on pharmaceutical and biotechnology regulatory and industry issues. Their web site is *www.fdcreports.com*.

- For books, the Interpharm press used to have an extensive catalogue, principally intended for the biopharmaceutical and drug industries, but also of interest to us. This company was acquired by CRC Press and their on-line catalogue has a number of useful volumes in the Pharmaceutical Science and Regulation segments. I should mention GLP Essentials by Milton Anderson, published in 2002. This is a concise guide suitable for training purposes. The Web address is *www.crcpress.com.*

Associations and Information Web Sites

The prime association in the USA is RAPS, the Regulatory Affairs Professionals Society (*www.raps.org*). This organizes conferences, runs training courses and publishes many useful items, including the monthly magazine for members and pocket versions of the CFR. Its counterpart in Canada is CAPRA (*www.capra.ca*).

GLP Consultants

It would not be appropriate in a guide like this to give the names of individual consultants specializing in this work about whom I know little or nothing. There are directories to consultants which can be accessed via the Internet, for example:

- GlobalRegulatory.com, a web site devoted to listing requests for regulatory assistance and providing access to consultants registered on the site.
- The Expert Market Place, at *www.ework-markets.com*
- ProSavvy, Inc. which has a web site devoted to bringing consultants and clients together at *www.prosavvy.com*

You will find that most of the consultants specialize in GMP and the type of compliance auditing and documentary work needed by companies working towards product approval for marketing, but any consultant worth talking to should be able to assist with GLP matters as well. Don't forget that well-known and highly respected consultants such as Barbara Immel and Nancy Chew write regular columns in *BioPHARM International* and *Pharmaceutical Technology*.

CHAPTER 9: APPENDICES

GLP Inspection Forms

The following set of forms is derived directly from the 21CFR 58 regulations. They can be copied directly from the book as needed. Each requirement is covered, so that filling in the questionnaire will ensure that every compliance factor is covered. For routine QA inspections, only certain sections need be used, particularly those on Protocol and Study Conduct, Test and Control Articles and Records.

Before an external inspection, e.g., by the FDA, it is advisable to conduct a full inspection, using the entire set of forms.

GOOD LABORATORY PRACTICE
INSPECTION REPORT
for
NON-CLINICAL LABORATORY STUDIES

(FDA:21CFR Ch 1 (4-1-03) Part 58)

Prepared for: _____

By: _____

Date: _____

Ref #:

GLP INSPECTION REPORT	
Non-clinical Study Inspected:	
Facility:	
Study Director:	
Sponsor:	
QA Inspector(s):	
Inspection Date:	
Report Prepared By:	
Date:	
Report Reviewed By:	
Date:	

Source: Derived from 21CFR58 Regulations.

Ref #

GLP INSPECTION REPORT					
Inspector: _____ Date: _____					
1.0 Personnel	Reg: 58.29	Yes	No	N/A	*Narrative
1.1 All personnel involved with the Non-Clinical Laboratory Study being inspected and each person's general responsibilities are listed.					
1.2 There are sufficient personnel for the timely and proper conduct of the study according to the protocol.					
1.3 Employees practice good sanitation and health habits to avoid contamination of test and control articles.					
1.4 Personnel engaged in a nonclinical laboratory study wear clothing that is appropriate for the duties they perform.					
1.5 All personnel are instructed to report any health or medical conditions that may have an adverse effect on a non-clinical laboratory study.					
Additional Narrative - List according to section number.					

Source: Derived from 21CFR58 Regulations.

Ref #

GLP INSPECTION REPORT					
Inspector: _____ Date: _____					
2.0 Testing Facility Management	Reg: 58.31	Yes	No	N/A	*Narrative
2.1 The Study Director is listed.					
2.2 Back-up or replacement for Study Director, if one exists, is listed.					
2.3 Testing facility management has assured that test and control articles or mixtures have been appropriately tested for identity, strength, purity, stability and uniformity.					
2.4 Personnel, resources, facilities, equipment, materials and methodologies are available as scheduled.					
2.5 Personnel clearly understand the functions they are to perform.					
2.6 QA unit is in place.					
2.7 Any deviations from CFR are reported by QA unit.					
Additional Narrative - List according to section number.					

Source: Derived from 21CFR58 Regulations.

Ref#:

GLP INSPECTION REPORT				
Inspector: _____ Date: _____				
3.0 Study Director's Responsibilities Reg: 58.33	Yes	No	N/A	*Narrative
3.1 The protocol, including any change, is approved by the Study Director.				
3.2 All experimental data, including observations of unanticipated responses of the test system, are accurately recorded and verified.				
3.3 Unforseen circumstances that may affect the quality and integrity of the study are noted when they occur and corrective action is taken and documented.				
3.4 Test systems are as specified in the protocol.				
3.5 All applicable GLP Regulations are followed.				
3.6 All data, documentation, protocols, specimens and final reports are transferred to the archives during or at the close of the study.				
Additional Narrative - List according to section number.				

Source: Derived from 21CFR58 Regulations.

Ref #:

GLP INSPECTION REPORT				
Inspector: _____ Date: _____				
4.0 Quality Assurance Unit Reg: 58.35	Yes	No	N/A	*Narrative
4.1 QA Unit is set up to monitor the study.				
4.2 QA Unit maintains copies of: Master schedule sheet of all studies Protocols of all studies.				
4.3 QA Unit inspects study at adequate intervals and maintains written records of the inspections.				
4.4 QA Unit submits periodical status reports on each study to management and the Study Director.				
4.5 QA Unit determines that no deviations from protocols or SOPs are made without proper authorization and documentation.				
4.6 QA Unit reviews final study report for accuracy and appends signed statement of inspections and findings reported.				
4.7 QA Unit's written responsibilities, procedures and records are properly maintained.				
Additional Narrative - List according to section number.				

Source: Derived from 21CFR58 Regulations.

Ref #:

GLP INSPECTION REPORT				
Inspector: _____ Date: _____				
5.0 Facilities, General Reg: 58.41	Yes	No	N/A	*Narrative
5.1 Testing facility if of suitable size, construction and is adequately separated from other facilities/functions.				
Additional Narrative - List according to section number.				

Source: Derived from 21CFR58 Regulations.

Ref #:

GLP INSPECTION REPORT				
Inspector: _____ Date: _____				
6.0 Animal Care Facilities Reg: 58.43	Yes	No	N/A	*Narrative
6.1 A sufficient number of animal rooms or areas are provided to ensure proper separation of species of test systems, to isolate individual projects, quarantine animals and for routine or specialized housing.				
6.2 Separate laboratory space is provided for the performance of specialized activities such aseptic surgery, intensive care, necropsy, and radiography.				
6.3 A number of animal rooms or areas are provided to ensure isolation of studies being done with test systems or test and control articles known to be biohazardous, including volatile substances, aerosols, radioactive materials and infectious agents.				
6.4 Separate areas are provided for the diagnosis, treatment and control of laboratory animal diseases. These areas provide effective isolation for animals either known or suspected of being diseased, or of being carriers of disease.				
6.5 When housing animals, facilities shall exist for the collection and disposal of all animal waste and refuse or for storage of waste before removal. Disposal facilities are provided and operated so as to minimize vermin infestation, odors, disease, hazards an environmental contamination.				
6.6 Animal facilities are designed to minimize disturbances that interfere with the study.				
Additional Narrative - List according to section number.				

Source: Derived from 21CFR58 Regulations.

Ref #:

GLP INSPECTION REPORT				
Inspector: _____ Date: _____				
7.0 Animal Supply Facilities Reg: 58.45	Yes	No	N/A	*Narrative
7.1 Storage areas, as needed for feed, bedding, supplies and equipment are provided.				
7.2 Storage areas for feed and bedding are separated from areas housing the test systems and are protected against infestation or contamination.				
7.3 Refrigeration is provided for perishable supplies or feed.				
Additional Narrative - List according to section number.				

Source: Derived from 21CFR58 Regulations.

Ref #:

GLP INSPECTION REPORT				
Inspector: _____ Date: _____				
8.0 Facilities for Handling Test and Control Articles Reg: 58.47	Yes	No	N/A	*Narrative
8.1 To prevent contamination or mixups there are separate areas for:				
8.1.1 Receipt and storage of the test and control articles.				
8.1.2 Mixing of the test and control articles with a carrier, e.g. feed.				
8.1.3 Storage of the test and control mixtures.				
8.2 Storage areas for the test and/or control article and test and control mixtures are separate from areas housing the test systems and shall be adequate to preserve the identity, strength, purity and stability of the articles and mixtures.				
Additional Narrative - List according to section number.				

Source: Derived from 21CFR58 Regulations.

Ref #:

GLP INSPECTION REPORT				
Inspector: _____ Date: _____				
9.0 Laboratory Operation Areas Reg: 58.49	Yes	No	N/A	*Narrative
9.1 Separate laboratory space is provided, as needed, for the performance of the routine procedures required by non- clinical laboratory studies including:				
9.1.1 Specialized areas for performing activities such as aseptic surgery, intensive care, necropsy, histology, radiography and handling of biohazardous materials.				
9.1.2 Separate space is provided for cleaning, sterilizing and maintaining equipment and supplies used during the course of the study.				
Additional Narrative - List according to section number.				

Source: Derived from 21CFR58 Regulations.

Ref#:

GLP INSPECTION REPORT				
Inspector: _____ Date: _____				
10.0 Specimen and Data Storage Reg: 58.51	Yes	No	N/A	*Narrative
10.1 Space is provided for archives limited to access by authorized personnel only, for the storage and retrieval of all raw data and specimens from completed studies.				
Additional Narrative - List according to section number.				

Source: Derived from 21CFR58 Regulations.

Ref #:

GLP INSPECTION REPORT				
Inspector: _____ Date:				
11.0 Administrative and Personnel Facilities Non-Reg:	Yes	No	N/A	*Narrative
11.1 There is space provided for the administration, supervision and direction of the testing facility.				
11.2 Separate space is provided for locker, shower, toilet and washing facilities, as needed.				
Additional Narrative - List according to section number.				

Source: Derived from 21CFR58 Regulations.

Ref #:

GLP INSPECTION REPORT				
Inspector: _____ Date: _____				
12.0 Equipment Reg: 58.61	Yes	No	N/A	*Narrative
12.1 Equipment design				
12.1.1 Equipment used in the generation, measurement or assessment of data and equipment used for facility environmental control is of appropriate design and adequate capacity.				
12.1.2 Equipment is suitably located for operation, inspection, cleaning and maintenance.				
12.2 Maintenance and Calibration				
12.2.1 Equipment is adequately inspected, cleaned and maintained, listed and calibrated and/or standardized.				
12.2.2 SOPs detail methods, materials and schedules to be used in the routine inspection, cleaning, maintenance, testing, calibration and/or standardization of equipment and specify remedial action in the event of failure.				
12.2.3 SOPs designate the person responsible for the performance of each operation.				
12.2.4 SOPs are available to laboratory personnel. Written records are maintained of all inspection, maintenance, testing, calibrating and/or standardizing operations. These records contain date, repairs performed, remedial action.				
Additional Narrative - List according to section number.				

Source: Derived from 21CFR58 Regulations.

Ref #:

GLP INSPECTION REPORT				
Inspector: _____ Date: _____				
13.0 Testing Facility Operation Reg: 58.81	Yes	No	N/A	*Narrative
13.1 Standard operating procedures are in writing which set forth non-clinical laboratory study methods adequate to ensure the quality and integrity of the data generated in the course of a study.				
13.2 Deviations from SOP are authorized by the study director and documented in the raw data.				
13.3 Significant changes in established SOPs are properly authorized in writing by management.				
13.4 SOPs are established for:				
13.4.1 Animal room preparation.				
13.4.2 Animal care.				
13.4.3 Receipt, identification, storage, handling, mixing and method of sampling of the test and control articles.				
13.4.4 Test system observations.				
13.4.5 Laboratory tests.				
13.4.6 Handling of animals found moribund or dead during study. Source: Derived from	21 CFR58			
13.4.7 Necropsy of animals or post mortem examination of animals.			Regulations	
13.4.8 Collection and identification of specimens.				
13.4.9 Histophathology.				
13.4.10 Data handling, storage and retrieval.				
13.4.11 Maintenance and calibration of equipment.				
13.4.12 Transfer, proper placement and identification of animals.				

13.5 Each laboratory area has a laboratory manual and SOPs relative to lab procedures, e.g. toxicology, histology, clinical chemistry, hematology, teratology, necropsy.				
13.6 A historical file of SOPs and all revisions thereof is maintained.				
Additional Narrative - List according to section number.				

Source: Derived from 21CFR58 Regulations.

Ref #:

GLP INSPECTION REPORT				
Inspector: _____ Date: _____				
14.0 Reagents and Solutions Reg: 58.83	Yes	No	N/A	*Narrative
14.1 Reagents and solutions in the laboratory areas are labeled to indicate identity, titer or concentration, storage requirements and expiration data.				
14.2 Deteriorated or out-dated reagents and solutions are not used.				
Additional Narrative - List according to section number.				

Source: Derived from 21CFR58 Regulations.

Ref #:

GLP INSPECTION REPORT				
Inspector: _____ Date: _____				
15.0 Animal Care Reg: 58.90	Yes	No	N/A	*Narrative
15.1 SOPs are available for the housing, feeding, handling and the care of animals.				
15.2 Newly received animals are placed in quarantine until their health status has been evaluated in accordance with acceptable veterinary medical practice.				
15.3 Animals are free of disease that might interfere with the study.				
15.4 Arrangements are in place for the isolation and treatment of animals that contract a disease during the course of a study.				
15.5 Animals are clearly identified to prevent mix-ups when different test groups of the same species are housed together.				
15.6 Animal cages, racks and accessory equipment are cleaned and sanitized at appropriate intervals.				
15.7 Food and water used for animals are analyzed to ensure contaminants are not at such levels as may interfere with the study.				
15.8 Bedding used in cages or pens does not interfere with the study.				
15.9 Pest control, if used, is documented and shall not interfere with the study.				
Additional Narrative - List according to section number.				

Source: Derived from 21CFR58 Regulations.

Ref #:

GLP INSPECTION REPORT				
Inspector: _____ Date: _____				
16.0 Test and Control Article Characterization Reg: 58.105	Yes	No	N/A	*Narrative
16.1 Each batch of a test and control substance is assayed for identity, strength, purity and composition prior to initiating the study by the laboratory or the sponsor who provides verifying documentation with the substances.				
16.2 Prior to initiation of the study, the stability of each test and control substance is determined where possible.				
16.3 If the stability of the test and control articles cannot be determined before initiation of a study, SOPs are established and followed to provide for periodic re-analysis of each batch.				
16.4 Storage containers for a test or control article are labeled by name, chemical abstract number or code number, batch number, expiration date, if any, and storage conditions when necessary to maintain the identity, strength, purity and composition of the test or control article.				
16.5 Storage containers are assigned to a particular test article for the duration of the study.				
16.6 For studies lasting more than four weeks, reserve samples from each batch of test and control articles are retained for the period of time specified in the section 58.195 of GLP Regs.				
Additional Narrative - List according to section number.				

Source: Derived from 21CFR58 Regulations.

Ref #:

GLP INSPECTION REPORT				
Inspector: _____ Date: _____				
17.0 Test and Control Article Handling Reg: 58.107	Yes	No	N/A	*Narrative
17.1 Procedures are established for a system of handling the test and control articles to ensure that:				
17.1.1 There is proper storage.				
17.1.2 Distribution is made in a manner designed to preclude the possibility of contamination, deterioration or damage.				
17.1.3 The receipt and distribution of each batch is documented. such documentation includes the date and quantity of each batch distributed or returned.				
Additional Narrative - List according to section number.				

Source: Derived from 21CFR58 Regulations.

Ref #:

GLP INSPECTION REPORT				
Inspector: _____ Date: _____				
18.0 Mixtures of Articles with Carriers Reg: 58.113	Yes	No	N/A	*Narrative
18.1 For each test or control article that is mixed with a carrier, tests by analytical methods are conducted to:				
18.1.1 Determine mixtures' uniformity and periodically determine the concentration of the test or control article in the mixture.				
18.1.2 Determine the stability of the test and control articles in the mixture. If stability cannot be determined before initiation of the study, SOPs are established and followed to provide for periodic re-analysis of the test and control articles in the mixture.				
18.1.3 For studies of more than four weeks duration a reserve sample of each test or control carrier article mixture is taken and retained for the period of time specified by section 58.195 of GLP Regs.				
18.1.4 If any of the components of the test or control article carrier mixture has an expiration date, that date is clearly shown on the container. If more than one component has an expiration date, the earliest date is shown.				
Additional Narrative - List according to section number.				

Source: Derived from 21CFR58 Regulations.

Ref #:

GLP INSPECTION REPORT				
Inspector: _____ Date: _____				
19.0 Protocol Reg: 58.120	Yes	No	N/A	*Narrative
19.1 Protocol is written and approved.				
19.2 Protocol contains:				
19.2.1 Descriptive title and statement of purpose of study.				
19.2.2 Names of test and control articles, chemical abstract number or code number.				
19.2.3 Sponsor's name and name and address of facility conducting this study.				
19.2.4 The proposed starting and completion dates.				
19.2.5 Justification for selection of the test system.				
19.2.6 Where applicable, the number, body weight, range, sex, source of supply, species strain, substrain and the age of animals in the test system.				
19.2.7 Procedure for identification of the test system.				
19.2.8 A description of the experimental design, including the methods for the control of bias.				
19.2.9 Identification of the animal diet and all materials included.				
19.2.10 Route of administration and the reason for its choice.				
19.2.11 Each dosage level, expressed in mg/kg of body weight or other appropriate units and the method and frequency of administration.				
19.2.12 Method by which the degree of absorption of the test and control articles by the test systems will be determined if necessary to achieve the objectives of the study.				
19.2.13 The type and frequency of tests, analysis and measurements to be made.				

19.2.14 The records to be maintained.				
19.2.15 A statement of the proposed statistical methods to be used.				
19.2.16 The date of approval of the protocol by the sponsor and the signature of the study director.				
19.3 Revisions of an approved protocol and the reasons shall be documented, signed by the study director, dated and maintained with the protocol.				
Additional Narrative - List according to section number.				

Source: Derived from 21CFR58 Regulations.

Ref #:

GLP INSPECTION REPORT				
Inspector: _____ Date: _____				
20.0 Conduct of a Non-clinical Laboratory Study Reg: 58.130	Yes	No	N/A	*Narrative
20.1 The study is conducted in accordance with the protocol.				
20.2 The test systems are monitored in conformity with the protocol.				
20.3 Specimens are identified by the test system, study, nature, and date of collection. This information is located on the specimen container or accompanies the specimen in a manner that precludes error in the recording and storage of data.				
20.4 Gross findings during post-mortem are recorded and made available to the pathologist when examining that specimen histopathologically.				
20.5 Data generated during the study, except direct computer input data, are recorded promptly and legibly in ink.				
20.6 Entries are dated on the day of entry and signed by the person entering the data.				
20.7 Changes in entries do not obscure original entry and are signed and dated.				
Additional Narrative - List according to section number.				

Source: Derived from 21CFR58 Regulations.

Ref #:

GLP INSPECTION REPORT				
Inspector: _____ Date: _____				
21.0 Reporting of Non-clinical Laboratory Study Results Reg: 58.185	Yes	No	N/A	*Narrative
21.1 The final report for the non-clinical laboratory study includes:				
21.1.1 Name and address of the facility performing the study.				
21.1.2 Dates on which the study was started and completed.				
21.1.3 Objectives and procedures stated in approved protocol including changes in the original protocol.				
21.1.4 Statistical methods employed for data analysis.				
2 1.1.5 The test and control articles by name, code number or chemical abstract number, strength and purity.				
21.1.6 Stability of the test and control articles under conditions of administration.				
21.1.7 Description of methods used.				
21.1.8 The test system used.				
21.1.9 If applicable, the number of animals used, sex, body weight, range, source of suply, species strain and substrain, age and procedure for identification.				
21.1.10 Description of the dosage regimen, administration route and duration.				
21.1.11 Unforseen circumstances that may have affected the quality or integrity of the non-clinical laboratory study.				
21.1.12 Names of the study director, other scientists, all supervisory personnel involved in the study.				
21.1.13 A description of the transformations, calculations, or operations performed on the data and conclusions drawn.				
21.1.14 The signed and dated reports of each scientist involved.				

21.1.15 Locations where all specimens, raw data and final report are to be stored.				
21.1.16 A statement prepared by the Quality Assurance Department on the Study Inspection and of findings reported to management and to the study director.				
21.1.17. The final report is signed by the study director.				
Additional Narrative - List according to section number.				

Source: Derived from 21CFR58 Regulations.

Ref #:

GLP INSPECTION REPORT				
Inspector: _____ Date: _____				
22.0 Storage and Retrieval of Records and Data Reg: 58.190	Yes	No	N/A	*Narrative
22.1 All raw data, documentation, protocols, reports and specimens (except wet specimens/biological fluids) are retained.				
22.2 Archives are maintained for the orderly storage and retrieval of the data, documentation and specimens.				
22.3 There is an individual responsible for these archives.				
22.4 The archives are indexed to permit expedient retrieval.				
22.5 Only authorized personnel may enter the archives.				
22.6 Archives and records of the master schedule sheet, protocols, QA inspections and personnel experience, training and job descriptions are retained according to the provisions of the CFR.				
Additional Narrative - List according to section number.				

Source: Derived from 21CFR58 Regulations.

Texts of GLP Regulations

Most of these documents are in the public domain and can be downloaded from the relevant Web sites. Permission has been received where necessary to reproduce the latest texts I have been able to access from the FDA, OECD and Japan. These are printed here verbatim; only the type font has been changed to achieve a measure of uniformity in the text. For ease of handling, each separate set of documents starts on a fresh page.

The following documents are reproduced:

USA

21CFR58	Good Laboratory Practice for Nonclinical Laboratory Studies, 2006
21CFR 11	Electronic Records; Electronic Signatures, 2003
	Final Guidance to 21CFR 11, August, 2003
	BioResearch Monitoring: Guidance Manual Part III

OECD

ENV/MC/CHEM(98) 17 Principles of Good Laboratory Practice, 1998

Japan

Ordinance 21 and PAB 424, 1997

GLP Standard Ordinance for Nonclinical Laboratory Studies on Safety of Drugs

US FDA 21CFR, Part 58

[Revised as of April 1, 2006]

TITLE 21—FOOD AND DRUGS

CHAPTER I—FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

PART 58—GOOD LABORATORY PRACTICE FOR NONCLINICAL LABORATORY STUDIES

Subpart A—General Provisions

Sec.

Subpart B—Organization and Personnel

Subpart C—Facilities

Subpart D—Equipment

58.61 Equipment design.

58.63 Maintenance and calibration of equipment.

Subpart E—Testing Facilities Operation

58.81 Standard operating procedures. 58.83 Reagents and solutions.

58.90 Animal care.

Subpart F—Test and Control Articles

58.105 Test and control article characterization.

58.107 Test and control article handling.

58. 113 Mixture of articles with carriers.

Subpart G—Protocol for and Conduct of a Nonclinical Laboratory Study

58.120 Protocol.

58.130 Conduct of a nonclinical laboratory study.

Subparts H-I—[Reserved]

Subpart J—Records and Reports

58.185 Reporting of nonclinical laboratory study results.

58.190 Storage and retrieval of records and data.

58.195 Retention of records.

Subpart K—Disqualification of Testing Facilities

58.200 Purpose.

58.202 Grounds for disqualification.

58.204 Notice of and opportunity for hearing on proposed disqualification.

58.206 Final order on disqualification.

58.210 Actions upon disqualification.

58.213 Public disclosure of information regarding disqualification. 58.215 Alternative or additional actions to disqualification.

58.217 Suspension or termination of a testing facility by a sponsor. 58.2 19 Reinstatement of a disqualified testing facility.

Authority: 21 U.S.C. 342, 346, 346a, 348, 351, 352, 353, 355, 360, 360b-360f, 360h-360j, 371, 379e, 381; 42 U.S.C. 216, 262, 263b-263n.

Source: 43 FR 60013, Dec. 22, 1978, unless otherwise noted.**Subpart A—General Provisions**

Sec. 58.1 Scope.

a) This part prescribes good laboratory practices for conducting nonclinical laboratory studies that support or are intended to support applications for research or marketing permits for products regulated by the Food and Drug Administration, including food and color additives, animal food additives, human and animal drugs, medical devices for human use, biological products, and electronic products. Compliance with this part is intended to assure the quality and integrity of the safety data filed pursuant to sections 406, 408, 409, 502, 503, 505, 506, 510, 512-516, 518-520, 721, and 801 of the Federal Food, Drug, and Cosmetic Act and sections 351 and 354-360F of the Public Health Service Act.

b) References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33779, Sept. 4, 1987; 64 FR 399, Jan. 5, 1999]

Sec. 58.3 Definitions.

As used in this part, the following terms shall have the meanings specified:

a) Act means the Federal Food, Drug, and Cosmetic Act, as amended (secs. 201-902, 52 Stat. 1040 et seq., as amended (21 U.S.C. 32 1-392)).

b) Test article means any food additive, color additive, drug, biological product, electronic product, medical device for human use, or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act.

c) Control article means any food additive, color additive, drug, biological product, electronic product, medical device for human use, or any article other than a test article, feed, or water that is administered to the test system in the course of a nonclinical laboratory study for the purpose of establishing a basis for comparison with the test article.

d) Nonclinical laboratory study means in vivo or in vitro experiments in which test articles are studied prospectively in test systems under laboratory conditions to determine their safety. The term does not include studies utilizing human subjects or clinical studies or field trials in animals. The term does not include basic exploratory studies carried out to determine whether a test article has any potential utility or to determine physical or chemical characteristics of a test article.

e) Application for research or marketing permit includes:

   1. A color additive petition, described in part 71.
   2. A food additive petition, described in parts 171 and 571.
   3. Data and information regarding a substance submitted as part of the procedures for

establishing that a substance is generally recognized as safe for use, which use resultsor may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food, described in Secs. 170.35 and 570.35.

4. Data and information regarding a food additive submitted as part of the procedures regarding food additives permitted to be used on an interim basis pending additional study, described in Sec. 180.1.
5. An investigational new drug application, described in part 312 of this chapter.
6. A new drug application, described in part 314.
7. Data and information regarding an over-the-counter drug for human use, submitted as part of the procedures for classifying such drugs as generally recognized as safe and effective and not misbranded, described in part 330.
8. Data and information about a substance submitted as part of the procedures for establishing a tolerance for unavoidable contaminants in food and food-packaging materials, described in parts 109 and 509.
9. [Reserved]
10. A Notice of Claimed Investigational Exemption for a New Animal Drug, described in part 511.
11. A new animal drug application, described in part 514.
12. [Reserved]
13. An application for a biologics license, described in part 601 of this chapter.
14. An application for an investigational device exemption, described in part 812.
15. An Application for Premarket Approval of a Medical Device, described in section 515 of the act.
16. A Product Development Protocol for a Medical Device, described in section 515 of the act.
17. Data and information regarding a medical device submitted as part of the procedures for classifying such devices, described in part 860.
18. Data and information regarding a medical device submitted as part of the procedures for establishing, amending, or repealing a performance standard for such devices, described in part 861.
19. Data and information regarding an electronic product submitted as part of the procedures for obtaining an exemption from notification of a radiation safety defect or failure of compliance with a radiation safety performance standard, described in subpart D of part 1003.

20. Data and information regarding an electronic product submitted as part of the procedures for establishing, amending, or repealing a standard for such product, described in section 358 of the Public Health Service Act.
21. Data and information regarding an electronic product submitted as part of the procedures for obtaining a variance from any electronic product performance standard as described in Sec. 1010.4.
22. Data and information regarding an electronic product submitted as part of the procedures for granting, amending, or extending an exemption from any electronic product performance standard, as described in Sec. 1010.5.
23. A premarket notification for a food contact substance, described in part 170, subpart D, of this chapter.

f) Sponsor means:

1. A person who initiates and supports, by provision of financial or other resources, a nonclinical laboratory study;
2. A person who submits a nonclinical study to the Food and Drug Administration in support of an application for a research or marketing permit; or
3. A testing facility, if it both initiates and actually conducts the study.

g) Testing facility means a person who actually conducts a nonclinical laboratory study, i.e., actually uses the test article in a test system. Testing facility includes any establishment required to register under section 510 of the act that conducts nonclinical laboratory studies and any consulting laboratory described in section 704 of the act that conducts such studies. Testing facility encompasses only those operational units that are being or have been used to conduct nonclinical laboratory studies.

h) Person includes an individual, partnership, corporation, association, scientific or academic establishment, government agency, or organizational unit thereof, and any other legal entity.

i) Test system means any animal, plant, microorganism, or subparts thereof to which the test or control article is administered or added for study. Test system also includes appropriate groups or components of the system not treated with the test or control articles.

j) Specimen means any material derived from a test system for examination or analysis.

k) Raw data means any laboratory worksheets, records, memoranda, notes, or exact copies thereof, that are the result of original observations and activities of a nonclinical laboratory study and are necessary for the reconstruction and evaluation of the report of that study. In the event that exact transcripts of raw data have been prepared (e.g., tapes which have been transcribed verbatim, dated, and verified accurate by signature), the exact copy or exact transcript may be

substituted for the original source as raw data. Raw data may include photographs, microfilm or microfiche copies, computer printouts, magnetic media, including dictated observations, and recorded data from automated instruments.

l) Quality assurance unit means any person or organizational element, except the study director, designated by testing facility management to perform the duties relating to quality assurance of nonclinical laboratory studies.

m) Study director means the individual responsible for the overall conduct of a nonclinical laboratory study.

n) Batch means a specific quantity or lot of a test or control article that has been characterized according to Sec. 58.105(a).

o) Study initiation date means the date the protocol is signed by the study director.

p) Study completion date means the date the final report is signed by the study director.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33779, Sept. 4, 1987; 54 FR 9039, Mar. 3, 1989; 64 FR 56448, Oct. 20, 1999; 67 FR 35729, May 21, 2002]

Sec. 58.10 Applicability to studies performed under grants and contracts.

When a sponsor conducting a nonclinical laboratory study intended to be submitted to or reviewed by the Food and Drug Administration utilizes the services of a consulting laboratory, contractor, or grantee to perform an analysis or other service, it shall notify the consulting laboratory, contractor, or grantee that the service is part of a nonclinical laboratory study that must be conducted in compliance with the provisions of this part.

Sec. 58.15 Inspection of a testing facility.

a) A testing facility shall permit an authorized employee of the Food and Drug Administration, at reasonable times and in a reasonable manner, to inspect the facility and to inspect (and in the case of records also to copy) all records and specimens required to be maintained regarding studies within the scope of this part. The records inspection and copying requirements shall not apply to quality assurance unit records of findings and problems, or to actions recommended and taken.

b) The Food and Drug Administration will not consider a nonclinical laboratory study in support of an application for a research or marketing permit if the testing facility refuses to permit inspection. The determination that a nonclinical laboratory study will not be considered in support of an application for a research or marketing permit does not, however, relieve the applicant for such a permit of any obligation under any applicable statute or regulation to submit the results of the study to the Food and Drug Administration.

Subpart B—Organization and Personnel

Sec. 58.29 Personnel.

a) Each individual engaged in the conduct of or responsible for the supervision of a nonclinical laboratory study shall have education, training, and experience, or combination thereof, to enable that individual to perform the assigned functions.

b) Each testing facility shall maintain a current summary of training and experience and job description for each individual engaged in or supervising the conduct of a nonclinical laboratory study.

c) There shall be a sufficient number of personnel for the timely and proper conduct of the study according to the protocol.

d) Personnel shall take necessary personal sanitation and health precautions designed to avoid contamination of test and control articles and test systems.

e) Personnel engaged in a nonclinical laboratory study shall wear clothing appropriate for the duties they perform. Such clothing shall be changed as often as necessary to prevent microbiological, radiological, or chemical contamination of test systems and test and control articles.

f) Any individual found at any time to have an illness that may adversely affect the quality and integrity of the nonclinical laboratory study shall be excluded from direct contact with test systems, test and control articles and any other operation or function that may adversely affect the study until the condition is corrected. All personnel shall be instructed to report to their immediate supervisors any health or medical conditions that may reasonably be considered to have an adverse effect on a nonclinical laboratory study.

Sec. 58.31 Testing facility management.

For each nonclinical laboratory study, testing facility management shall:

a) Designate a study director as described in Sec. 58.33, before the study is initiated.

b) Replace the study director promptly if it becomes necessary to do so during the conduct of a study.

c) Assure that there is a quality assurance unit as described in Sec. 58.35.

d) Assure that test and control articles or mixtures have been appropriately tested for identity, strength, purity, stability, and uniformity, as applicable.

e) Assure that personnel, resources, facilities, equipment, materials, and methodologies are available as scheduled.

f) Assure that personnel clearly understand the functions they are to perform.

g) Assure that any deviations from these regulations reported by the quality assurance unit are communicated to the study director and corrective actions are taken and documented.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33780, Sept. 4, 1987]

Sec. 58.33 Study director.

For each nonclinical laboratory study, a scientist or other professional of appropriate education, training, and experience, or combination thereof, shall be identified as the study director. The study director has 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. The study director shall assure that:

a) The protocol, including any change, is approved as provided by Sec. 58.120 and is followed.

b) All experimental data, including observations of unanticipated responses of the test system are accurately recorded and verified.

c) Unforeseen circumstances that may affect the quality and integrity of the nonclinical laboratory study are noted when they occur, and corrective action is taken and documented.

d) Test systems are as specified in the protocol.

e) All applicable good laboratory practice regulations are followed.

f) All raw data, documentation, protocols, specimens, and final reports are transferred to the archives during or at the close of the study.

[43 FR 60013, Dec. 22, 1978; 44 FR 17657, Mar. 23, 1979]

Sec. 58.35 Quality assurance unit.

a) A testing facility shall have a quality assurance unit which shall be responsible for monitoring each study to assure management that the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with the regulations in this part. For any given study, the quality assurance unit shall be entirely separate from and independent of the personnel engaged in the direction and conduct of that study.

b) The quality assurance unit shall:

1. Maintain a copy of a master schedule sheet of all nonclinical laboratory studies conducted at the testing facility indexed by test article and containing the test system, nature of study, date study was initiated, current status of each study, identity of the sponsor, and name of the study director.
2. Maintain copies of all protocols pertaining to all nonclinical laboratory studies for which the

unit is responsible.

3. Inspect each nonclinical laboratory study at intervals adequate to assure the integrity of the study and maintain written and properly signed records of each periodic inspection showing the date of the inspection, the study inspected, the phase or segment of the study inspected, the person performing the inspection, findings and problems, action recommended and taken to resolve existing problems, and any scheduled date for reinspection. Any problems found during the course of an inspection which are likely to affect study integrity shall be brought to the attention of the study director and management immediately.
4. Periodically submit to management and the study director written status reports on each study, noting any problems and the corrective actions taken.
5. Determine that no deviations from approved protocols or standard operating procedures were made without proper authorization and documentation.
6. Review the final study report to assure that such report accurately describes the methods and standard operating procedures, and that the reported results accurately reflect the raw data of the nonclinical laboratory study.
7. Prepare and sign a statement to be included with the final study report which shall specify the dates inspections were made and findings reported to management and to the study director.

c) The responsibilities and procedures applicable to the quality assurance unit, the records maintained by the quality assurance unit, and the method of indexing such records shall be in writing and shall be maintained. These items including inspection dates, the study inspected, the phase or segment of the study inspected, and the name of the individual performing the inspection shall be made available for inspection to authorized employees of the Food and Drug Administration.

d) A designated representative of the Food and Drug Administration shall have access to the written procedures established for the inspection and may request testing facility management to certify that inspections are being implemented, performed, documented, and followed-up in accordance with this paragraph.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33780, Sept. 4, 1987; 67 FR 9585, Mar. 4, 2002]

Subpart C—Facilities

Sec. 58.41 General.

Each testing facility shall be of suitable size and construction to facilitate the proper conduct of nonclinical laboratory studies. It shall be designed so that there is a degree of separation that will prevent any function or activity from having an adverse effect on the study.

[52 FR 33780, Sept. 4, 1987]

Sec. 58.43 Animal care facilities.

a) A testing facility shall have a sufficient number of animal rooms or areas, as needed, to assure proper: (1) Separation of species or test systems, (2) isolation of individual projects, (3) quarantine of animals, and (4) routine or specialized housing of animals.

b) A testing facility shall have a number of animal rooms or areas separate from those described in paragraph (a) of this section to ensure isolation of studies being done with test systems or test and control articles known to be biohazardous, including volatile substances, aerosols, radioactive materials, and infectious agents.

c) Separate areas shall be provided, as appropriate, for the diagnosis, treatment, and control of laboratory animal diseases. These areas shall provide effective isolation for the housing of animals either known or suspected of being diseased, or of being carriers of disease, from other animals.

d) When animals are housed, facilities shall exist for the collection and disposal of all animal waste and refuse or for safe sanitary storage of waste before removal from the testing facility. Disposal facilities shall be so provided and operated as to minimize vermin infestation, odors, disease hazards, and environmental contamination.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33780, Sept. 4, 1987]

Sec. 58.45 Animal supply facilities.

There shall be storage areas, as needed, for feed, bedding, supplies, and equipment. Storage areas for feed and bedding shall be separated from areas housing the test systems and shall be protected against infestation or contamination. Perishable supplies shall be preserved by appropriate means.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33780, Sept. 4, 1987]

Sec. 58.47 Facilities for handling test and control articles.

a) As necessary to prevent contamination or mixups, there shall be separate areas for:

1. Receipt and storage of the test and control articles.
2. Mixing of the test and control articles with a carrier, e.g., feed.
3. Storage of the test and control article mixtures.

b) Storage areas for the test and/or control article and test and control mixtures shall be separate from areas housing the test systems and shall be adequate to preserve the identity, strength, purity, and stability of the articles and mixtures.

Sec. 58.49 Laboratory operation areas.

Separate laboratory space shall be provided, as needed, for the performance of the routine and specialized procedures required by nonclinical laboratory studies.

[52 FR 33780, Sept. 4, 1987]

Sec. 58.51 Specimen and data storage facilities.

Space shall be provided for archives, limited to access by authorized personnel only, for the storage and retrieval of all raw data and specimens from completed studies.

Subpart D—Equipment

Sec. 58.61 Equipment design.

Equipment used in the generation, measurement, or assessment of data and equipment used for facility environmental control shall be of appropriate design and adequate capacity to function according to the protocol and shall be suitably located for operation, inspection, cleaning, and maintenance.

[52 FR 33780, Sept. 4, 1987]

Sec. 58.63 Maintenance and calibration of equipment.

a) Equipment shall be adequately inspected, cleaned, and maintained. Equipment used for the generation, measurement, or assessment of data shall be adequately tested, calibrated and/or standardized.

b) The written standard operating procedures required under Sec. 58.81(b) (11) shall set forth in sufficient detail the methods, materials, and schedules to be used in the routine inspection, cleaning, maintenance, testing, calibration, and/or standardization of equipment, and shall specify, when appropriate, remedial action to be taken in the event of failure or malfunction of equipment. The written standard operating procedures shall designate the person responsible for the performance of each operation.

c) Written records shall be maintained of all inspection, maintenance, testing, calibrating and/ or standardizing operations. These records, containing the date of the operation, shall describe whether the maintenance operations were routine and followed the written standard operating procedures. Written records shall be kept of nonroutine repairs performed on equipment as a result of failure and malfunction. Such records shall document the nature of the defect, how and when the defect was discovered, and any remedial action taken in response to the defect.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33780, Sept. 4, 1987; 67 FR 9585, Mar. 4, 2002]

Subpart E—Testing Facilities Operation

Sec. 58.81 Standard operating procedures.

a) A testing facility shall have standard operating procedures in writing setting forth nonclinical laboratory study methods that management is satisfied are adequate to insure the quality and integrity of the data generated in the course of a study. All deviations in a study from standard operating procedures shall be authorized by the study director and shall be documented in the raw data. Significant changes in established standard operating procedures shall be properly authorized in writing by management.

b) Standard operating procedures shall be established for, but not limited to, the following:

1. Animal room preparation.
2. Animal care.
3. Receipt, identification, storage, handling, mixing, and method of sampling of the test and control articles.
4. Test system observations.
5. Laboratory tests.
6. Handling of animals found moribund or dead during study.
7. Necropsy of animals or postmortem examination of animals.
8. Collection and identification of specimens.
9. Histopathology.
10. Data handling, storage, and retrieval.
11. Maintenance and calibration of equipment.
12. Transfer, proper placement, and identification of animals.

c) Each laboratory area shall have immediately available laboratory manuals and standard operating procedures relative to the laboratory procedures being performed. Published literature may be used as a supplement to standard operating procedures.

d) A historical file of standard operating procedures, and all revisions thereof, including the dates of such revisions, shall be maintained.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33780, Sept. 4, 1987] Sec. 58.83 Reagents and solutions.

All reagents and solutions in the laboratory areas shall be labeled to indicate identity, titer or concentration, storage requirements, and expiration date. Deteriorated or outdated reagents and solutions shall not be used.

Sec. 58.90 Animal care.

There shall be standard operating procedures for the housing, feeding, handling, and care of animals.

All newly received animals from outside sources shall be isolated and their health status shall be evaluated in accordance with acceptable veterinary medical practice.

At the initiation of a nonclinical laboratory study, animals shall be free of any disease or condition that might interfere with the purpose or conduct of the study. If, during the course of the study, the animals contract such a disease or condition, the diseased animals shall be isolated, if necessary. These animals may be treated for disease or signs of disease provided that such treatment does not interfere with the study. The diagnosis, authorizations of treatment, description of treatment, and each date of treatment shall be documented and shall be retained.

Warm-blooded animals, excluding suckling rodents, used in laboratory procedures that require manipulations and observations over an extended period of time or in studies that require the animals to be removed from and returned to their home cages for any reason (e.g., cage cleaning, treatment, etc.), shall receive appropriate identification. All information needed to specifically identify each animal within an animal-housing unit shall appear on the outside of that unit.

e) Animals of different species shall be housed in separate rooms when necessary. Animals of the same species, but used in different studies, should not ordinarily be housed in the same room when inadvertent exposure to control or test articles or animal mixup could affect the outcome of either study. If such mixed housing is necessary, adequate differentiation by space and identification shall be made.

f) Animal cages, racks and accessory equipment shall be cleaned and sanitized at appropriate intervals.

g) Feed and water used for the animals shall be analyzed periodically to ensure that contaminants known to be capable of interfering with the study and reasonably expected to be present in such feed or water are not present at levels above those specified in the protocol. Documentation of such analyses shall be maintained as raw data.

h) Bedding used in animal cages or pens shall not interfere with the purpose or conduct of the study and shall be changed as often as necessary to keep the animals dry and clean.

i) If any pest control materials are used, the use shall be documented. Cleaning and pest control

materials that interfere with the study shall not be used.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33780, Sept. 4, 1987; 54 FR 15924, Apr. 20, 1989; 56 FR 32088, July 15, 1991; 67 FR 9585, Mar. 4, 2002]

Subpart F—Test and Control Articles

Sec. 58.105 Test and control article characterization.

a) The identity, strength, purity, and composition or other characteristics which will appropriately define the test or control article shall be determined for each batch and shall be documented. Methods of synthesis, fabrication, or derivation of the test and control articles shall be documented by the sponsor or the testing facility. In those cases where marketed products are used as control articles, such products will be characterized by their labeling.

b) The stability of each test or control article shall be determined by the testing facility or by the sponsor either: (1) Before study initiation, or (2) concomitantly according to written standard operating procedures, which provide for periodic analysis of each batch.

c) Each storage container for a test or control article shall be labeled by name, chemical abstract number or code number, batch number, expiration date, if any, and, where appropriate, storage conditions necessary to maintain the identity, strength, purity, and composition of the test or control article. Storage containers shall be assigned to a particular test article for the duration of the study.

d) For studies of more than 4 weeks' duration, reserve samples from each batch of test and control articles shall be retained for the period of time provided by Sec. 58.195.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33781, Sept. 4, 1987; 67 FR 9585, Mar. 4, 2002]

Sec. 58.107 Test and control article handling.

Procedures shall be established for a system for the handling of the test and control articles to ensure that:

a) There is proper storage.

b) Distribution is made in a manner designed to preclude the possibility of contamination, deterioration, or damage.

c) Proper identification is maintained throughout the distribution process.

d) The receipt and distribution of each batch is documented. Such documentation shall include the date and quantity of each batch distributed or returned.

Sec. 58.113 Mixtures of articles with carriers.

a) For each test or control article that is mixed with a carrier, tests by appropriate analytical methods shall be conducted:

1) To determine the uniformity of the mixture and to determine, periodically, the concentration of the test or control article in the mixture.
2) To determine the stability of the test and control articles in the mixture as required by the conditions of the study either:
   i. Before study initiation, or
   ii. Concomitantly according to written standard operating procedures which provide for periodic analysis of the test and control articles in the mixture.

b) [Reserved]

c) Where any of the components of the test or control article carrier mixture has an expiration date, that date shall be clearly shown on the container. If more than one component has an expiration date, the earliest date shall be shown.

[43 FR 60013, Dec. 22, 1978, as amended at 45 FR 24865, Apr. 11, 1980; 52 FR 33781, Sept. 4, 1987]

Subpart G—Protocol for and Conduct of a Nonclinical Laboratory Study

Sec. 58.120 Protocol.

a) Each study shall have an approved written protocol that clearly indicates the objectives and all methods for the conduct of the study. The protocol shall contain, as applicable, the following information:

1. A descriptive title and statement of the purpose of the study.
2. Identification of the test and control articles by name, chemical abstract number, or code number.
3. The name of the sponsor and the name and address of the testing facility at which the study is being conducted.
4. The number, body weight range, sex, source of supply, species, strain, substrain, and age of the test system.
5. The procedure for identification of the test system.
6. A description of the experimental design, including the methods for the control of bias.
7 A description and/or identification of the diet used in the study as well as solvents, emulsifiers, and/or other materials used to solubilize or suspend the test or control articles before mixing with the carrier. The description shall include specifications for acceptable levels of contaminants that are reasonably expected to be present in the dietary materials and

are known to be capable of interfering with the purpose or conduct of the study if present at levels greater than established by the specifications.

8. Each dosage level, expressed in milligrams per kilogram of body weight or other appropriate units, of the test or control article to be administered and the method and frequency of administration.
9. The type and frequency of tests, analyses, and measurements to be made.
10. The records to be maintained.
11. The date of approval of the protocol by the sponsor and the dated signature of the study director.
12. A statement of the proposed statistical methods to be used.

b) All changes in or revisions of an approved protocol and the reasons therefor shall be documented, signed by the study director, dated, and maintained with the protocol.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33781, Sept. 4, 1987; 67 FR 9585, Mar. 4, 2002]

Sec. 58.130 Conduct of a nonclinical laboratory study.

a) The nonclinical laboratory study shall be conducted in accordance with the protocol.

b) The test systems shall be monitored in conformity with the protocol.

c) Specimens shall be identified by test system, study, nature, and date of collection. This information shall be located on the specimen container or shall accompany the specimen in a manner that precludes error in the recording and storage of data.

d) Records of gross findings for a specimen from postmortem observations should be available to a pathologist when examining that specimen histopathologically.

e) All data generated during the conduct of a nonclinical laboratory study, except those that are generated by automated data collection systems, shall be recorded directly, promptly, and legibly in ink. All data entries shall be dated on the date of entry and signed or initialed by the person entering the data. Any change in entries shall be made so as not to obscure the original entry, shall indicate the reason for such change, and shall be dated and signed or identified at the time of the change. In automated data collection systems, the individual responsible for direct data input shall be identified at the time of data input. Any change in automated data entries shall be made so as not to obscure the original entry, shall indicate the reason for change, shall be dated, and the responsible individual shall be identified.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33781, Sept. 4, 1987; 67 FR 9585, Mar. 4, 2002]

Subparts H-I— [Reserved]

Subpart J—Records and Reports

Sec. 58.185 Reporting of nonclinical laboratory study results.

a) A final report shall be prepared for each nonclinical laboratory study and shall include, but not necessarily be limited to, the following:

1. Name and address of the facility performing the study and the dates on which the study was initiated and completed.
2. Objectives and procedures stated in the approved protocol, including any changes in the original protocol.
3. Statistical methods employed for analyzing the data.
4. The test and control articles identified by name, chemical abstracts number or code number, strength, purity, and composition or other appropriate characteristics.
5. Stability of the test and control articles under the conditions of administration.
6. A description of the methods used.
7. A description of the test system used. Where applicable, the final report shall include the number of animals used, sex, body weight range, source of supply, species, strain and substrain, age, and procedure used for identification.
8. A description of the dosage, dosage regimen, route of administration, and duration.
9. A description of all circumstances that may have affected the quality or integrity of the data.
10. The name of the study director, the names of other scientists or professionals, and the names of all supervisory personnel, involved in the study.
11. A description of the transformations, calculations, or operations performed on the data, a summary and analysis of the data, and a statement of the conclusions drawn from the analysis.
12. The signed and dated reports of each of the individual scientists or other professionals involved in the study.
13. The locations where all specimens, raw data, and the final report are to be stored.
14. The statement prepared and signed by the quality assurance unit as described in Sec. 58.35(b)(7).

b) The final report shall be signed and dated by the study director.

c) Corrections or additions to a final report shall be in the form of an amendment by the study director. The amendment shall clearly identify that part of the final report that is being added to or corrected and the reasons for the correction or addition, and shall be signed and dated by the person responsible.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33781, Sept. 4, 1987]

Sec. 58.190 Storage and retrieval of records and data.

a) All raw data, documentation, protocols, final reports, and specimens (except those specimens obtained from mutagenicity tests and wet specimens of blood, urine, feces, and biological fluids) generated as a result of a nonclinical laboratory study shall be retained.

b) There shall be archives for orderly storage and expedient retrieval of all raw data, documentation, protocols, specimens, and interim and final reports. Conditions of storage shall minimize deterioration of the documents or specimens in accordance with the requirements for the time period of their retention and the nature of the documents or specimens. A testing facility may contract with commercial archives to provide a repository for all material to be retained. Raw data and specimens may be retained elsewhere provided that the archives have specific reference to those other locations.

c) An individual shall be identified as responsible for the archives.

d) Only authorized personnel shall enter the archives.

e) Material retained or referred to in the archives shall be indexed to permit expedient retrieval.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33781, Sept. 4, 1987; 67 FR 9585, Mar. 4, 2002]

Sec. 58.195 Retention of records.

a) Record retention requirements set forth in this section do not supersede the record retention requirements of any other regulations in this chapter.

b) Except as provided in paragraph (c) of this section, documentation records, raw data and specimens pertaining to a nonclinical laboratory study and required to be made by this part shall be retained in the archive(s) for whichever of the following periods is shortest:

1. A period of at least 2 years following the date on which an application for a research or marketing permit, in support of which the results of the nonclinical laboratory study were submitted, is approved by the Food and Drug Administration. This requirement does not apply to studies supporting investigational new drug applications (IND's) or applications for investigational device exemptions (IDE's), records of which shall be governed by the provisions of paragraph (b) (2) of this section.

2. A period of at least 5 years following the date on which the results of the nonclinical laboratory study are submitted to the Food and Drug Administration in support of an application for a research or marketing permit.

3. In other situations (e.g., where the nonclinical laboratory study does not result in the submission of the study in support of an application for a research or marketing permit), a period of at least 2 years following the date on which the study is completed, terminated, or discontinued.

a) Wet specimens (except those specimens obtained from mutagenicity tests and wet specimens of blood, urine, feces, and biological fluids), samples of test or control articles, and specially prepared material, which are relatively fragile and differ markedly in stability and quality during storage, shall be retained only as long as the quality of the preparation affords evaluation. In no case shall retention be required for longer periods than those set forth in paragraphs (a) and (b) of this section.
b) The master schedule sheet, copies of protocols, and records of quality assurance inspections, as required by Sec. 58.3 5(c) shall be maintained by the quality assurance unit as an easily accessible system of records for the period of time specified in paragraphs (a) and (b) of this section.
c) Summaries of training and experience and job descriptions required to be maintained by Sec. 58.29(b) may be retained along with all other testing facility employment records for the length of time specified in paragraphs (a) and (b) of this section.
d) Records and reports of the maintenance and calibration and inspection of equipment, as required by Sec. 58.63(b) and (c), shall be retained for the length of time specified in paragraph (b) of this section.
e) Records required by this part may be retained either as original records or as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records.
f) If a facility conducting nonclinical testing goes out of business, all raw data, documentation, and other material specified in this section shall be transferred to the archives of the sponsor of the study. The Food and Drug Administration shall be notified in writing of such a transfer.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33781, Sept. 4, 1987; 54 FR 9039, Mar. 3, 1989]

Subpart K—Disqualification of Testing Facilities

Sec. 58.200 Purpose.

a) The purposes of disqualification are:

1) To permit the exclusion from consideration of completed studies that were conducted by a testing facility which has failed to comply with the requirements of the good laboratory practice regulations until it can be adequately demonstrated that such noncompliance did not occur during, or did not affect the validity or acceptability of data generated by, a particular study; and
2) To exclude from consideration all studies completed after the date of disqualification until the facility can satisfy the Commissioner that it will conduct studies in compliance with such regulations.

b) The determination that a nonclinical laboratory study may not be considered in support of an application for a research or marketing permit does not, however, relieve the applicant for such a permit of any obligation under any other applicable regulation to submit the results of the study to the Food and Drug Administration.

Sec. 58.202 Grounds for disqualification.

The Commissioner may disqualify a testing facility upon finding all of the following:

a) The testing facility failed to comply with one or more of the regulations set forth in this part (or any other regulations regarding such facilities in this chapter);
b) The noncompliance adversely affected the validity of the nonclinical laboratory studies; and
c) Other lesser regulatory actions (e.g., warnings or rejection of individual studies) have not been or will probably not be adequate to achieve compliance with the good laboratory practice regulations.

Sec. 58.204 Notice of and opportunity for hearing on proposed disqualification.

a) Whenever the Commissioner has information indicating that grounds exist under Sec. 58.202 which in his opinion justify disqualification of a testing facility, he may issue to the testing facility a written notice proposing that the facility be disqualified.
b) A hearing on the disqualification shall be conducted in accordance with the requirements for a regulatory hearing set forth in part 16 of this chapter.

Sec. 58.206 Final order on disqualification.

a) If the Commissioner, after the regulatory hearing, or after the time for requesting a hearing expires without a request being made, upon an evaluation of the administrative record of the disqualification proceeding, makes the findings required in Sec. 58.202, he shall issue a final order disqualifying the facility. Such order shall include a statement of the basis for that determination. Upon issuing a final order, the Commissioner shall notify (with a copy of the order) the testing facility of the action.

b) If the Commissioner, after a regulatory hearing or after the time for requesting a hearing expires without a request being made, upon an evaluation of the administrative record of the disqualification proceeding, does not make the findings required in Sec. 58.202, he shall issue a final order terminating the disqualification proceeding. Such order shall include a statement of the basis for that determination.

Upon issuing a final order the Commissioner shall notify the testing facility and provide a copy of the order.

Sec. 58.210 Actions upon disqualification.

a) Once a testing facility has been disqualified, each application for a research or marketing permit, whether approved or not, containing or relying upon any nonclinical laboratory study conducted by the disqualified testing facility may be examined to determine whether such study was or would be essential to a decision. If it is determined that a study was or would be essential, the Food and Drug Administration shall also determine whether the study is acceptable, notwithstanding the disqualification of the facility. Any study done by a testing facility before or after disqualification may be presumed to be unacceptable, and the person relying on the study may be required to establish that the study was not affected by the circumstances that led to the disqualification, e.g., by submitting validating information. If the study is then determined to be unacceptable, such data will be eliminated from consideration in support of the application; and such elimination may serve as new information justifying the termination or withdrawal of approval of the application.

b) No nonclinical laboratory study begun by a testing facility after the date of the facility's disqualification shall be considered in support of any application for a research or marketing permit, unless the facility has been reinstated under Sec. 58.2 19. The determination that a study may not be considered in support of an application for a research or marketing permit does not, however, relieve the applicant for such a permit of any obligation under any other applicable regulation to submit the results of the study to the Food and Drug Administration.

[43 FR 60013, Dec. 22, 1978, as amended at 59 FR 13200, Mar. 21, 1994]

Sec. 58.213 Public disclosure of information regarding disqualification.

a) Upon issuance of a final order disqualifying a testing facility under Sec. 58.206(a), the Commissioner may notify all or any interested persons. Such notice may be given at the discretion of the Commissioner whenever he believes that such disclosure would further the public interest or would promote compliance with the good laboratory practice regulations set forth in this part. Such notice, if given, shall include a copy of the final order issued under Sec. 58.206(a) and shall state that the disqualification constitutes a determination by the Food and Drug Administration that nonclinical laboratory studies performed by the facility will not be considered by the Food and Drug Administration in support of any application for a research or marketing permit. If such notice is sent to another Federal Government agency, the Food and Drug Administration will recommend that the agency also consider whether or not it should accept nonclinical laboratory studies performed by the testing facility. If such notice is sent to any other person, it shall state that it is given because of the relationship between the testing facility and the person being notified and that the Food and Drug Administration is not advising or recommending that any action be taken by the person notified.

b) A determination that a testing facility has been disqualified and the administrative record regarding such determination are disclosable to the public under part 20 of this chapter.

Sec. 58.215 Alternative or additional actions to disqualification.

a) Disqualification of a testing facility under this subpart is independent of, and neither in lieu of nor a precondition to, other proceedings or actions authorized by the act. The Food and Drug Administration may, at any time, institute against a testing facility and/or against the sponsor of a nonclinical laboratory study that has been submitted to the Food and Drug Administration any appropriate judicial proceedings (civil or criminal) and any other appropriate regulatory action, in addition to or in lieu of, and prior to, simultaneously with, or subsequent to, disqualification. The Food and Drug Administration may also refer the matter to another Federal, State, or local government law enforcement or regulatory agency for such action as that agency deems appropriate.

b) The Food and Drug Administration may refuse to consider any particular nonclinical laboratory study in support of an application for a research or marketing permit, if it finds that the study was not conducted in accordance with the good laboratory practice regulations set forth in this part, without disqualifying the testing facility that conducted the study or undertaking other regulatory action.

Sec. 58.217 Suspension or termination of a testing facility by a sponsor.

Termination of a testing facility by a sponsor is independent of, and neither in lieu of nor a precondition to, proceedings or actions authorized by this subpart. If a sponsor terminates or suspends a testing facility from further participation in a nonclinical laboratory study that is being conducted as part of any application for a research or marketing permit that has been submitted to any Center of the Food and Drug Administration (whether approved or not), it shall notify that Center in writing within 15 working days of the action; the notice shall include a statement of the reasons for such action. Suspension or termination of a testing facility by a sponsor does not relieve it of any obligation under any other applicable regulation to submit the results of the study to the Food and Drug Administration.

[43 FR FR 60013, Dec. 22, 1978, as amended at 50 FR 8995, Mar. 6, 1985] Sec. 58.219 Reinstatement of a disqualified testing facility.

A testing facility that has been disqualified may be reinstated as an acceptable source of nonclinical laboratory studies to be submitted to the Food and Drug Administration if the Commissioner determines, upon an evaluation of the submission of the testing facility, that the facility can adequately assure that it will conduct future nonclinical laboratory studies in compliance with the good laboratory practice regulations set forth in this part and, if any studies are currently being conducted, that the quality and integrity of such studies have not been seriously compromised. A disqualified testing facility that wishes to be so reinstated shall present in writing to the Commissioner reasons why it believes it should be reinstated and a detailed description of the corrective actions it has taken or intends to take to assure that the acts or

omissions which led to its disqualification will not recur. The Commissioner may condition reinstatement upon the testing facility being found in compliance with the good laboratory practice regulations upon an inspection. If a testing facility is reinstated, the Commissioner shall so notify the testing facility and all organizations and persons who were notified, under Sec. 58.213 of the disqualification of the testing facility. A determination that a testing facility has been reinstated is disclosable to the public under part 20 of this chapter.

USA 21CFR Part 11

[Revised as of April 1, 2003]

TITLE 21—FOOD AND DRUGS

CHAPTER I—FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

PART 11—ELECTRONIC RECORDS; ELECTRONIC SIGNATURES Subpart A—General Provisions

Sec.

Authority: 21 U.S.C. 32 1-393; 42 U.S.C. 262.

Source: 62 FR 13464, Mar. 20, 1997, unless otherwise noted.

Subpart A—General Provisions

Sec. 11.1 Scope.

a) The regulations in this part set forth the criteria under which the agency considers electronic records, electronic signatures, and handwritten signatures executed to electronic records to be trustworthy, reliable, and generally equivalent to paper records and handwritten signatures

executed on paper.

b) This part applies to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted, under any records requirements set forth in agency regulations. This part also applies to electronic records submitted to the agency under requirements of the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, even if such records are not specifically identified in agency regulations. However, this part does not apply to paper records that are, or have been, transmitted by electronic means.

c) Where electronic signatures and their associated electronic records meet the requirements of this part, the agency will consider the electronic signatures to be equivalent to full handwritten signatures, initials, and other general signings as required by agency regulations, unless specifically excepted by regulation(s) effective on or after August 20, 1997.

d) Electronic records that meet the requirements of this part may be used in lieu of paper records, in accordance with Sec. 11.2, unless paper records are specifically required.

e) Computer systems (including hardware and software), controls, and attendant documentation maintained under this part shall be readily available for, and subject to, FDA inspection.

Sec. 11.2 Implementation.

a) For records required to be maintained but not submitted to the agency, persons may use electronic records in lieu of paper records or electronic signatures in lieu of traditional signatures, in whole or in part, provided that the requirements of this part are met.

b) For records submitted to the agency, persons may use electronic records in lieu of paper records or electronic signatures in lieu of traditional signatures, in whole or in part, provided that:

1. The requirements of this part are met; and
2. The document or parts of a document to be submitted have been identified in public docket No. 92S-0251 as being the type of submission the agency accepts in electronic form. This docket will identify specifically what types of documents or parts of documents are acceptable for submission in electronic form without paper records and the agency receiving unit(s) (e.g., specific center, office, division, branch) to which such submissions may be made. Documents to agency receiving unit(s) not specified in the public docket will not be considered as official if they are submitted in electronic form; paper forms of such documents will be considered as official and must accompany any electronic records. Persons are expected to consult with the intended agency receiving unit for details on how (e.g., method of transmission, media, file formats, and technical protocols) and whether to proceed with the electronic submission.

Sec. 11.3 Definitions.

a) The definitions and interpretations of terms contained in section 201 of the act apply to those

terms when used in this part.

b) The following definitions of terms also apply to this part:

1 Act means the Federal Food, Drug, and Cosmetic Act (secs. 201-903 (21 U.S.C. 32 1-393)).

2. Agency means the Food and Drug Administration.

3. Biometrics means a method of verifying an individual's identity based on measurement of the individual's physical feature(s) or repeatable action(s) where those features and/ or actions are both unique to that individual and measurable.

4. Closed system means an environment in which system access is controlled by persons who are responsible for the content of electronic records that are on the system.

5. Digital signature means an electronic signature based upon cryptographic methods of originator authentication, computed by using a set of rules and a set of parameters such that the identity of the signer and the integrity of the data can be verified.

6. Electronic record means any combination of text, graphics, data, audio, pictorial, or other information representation in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system.

7. Electronic signature means a computer data compilation of any symbol or series of symbols executed, adopted, or authorized by an individual to be the legally binding equivalent of the individual's handwritten signature.

8. Handwritten signature means the scripted name or legal mark of an individual handwritten by that individual and executed or adopted with the present intention to authenticate a writing in a permanent form. The act of signing with a writing or marking instrument such as a pen or stylus is preserved. The scripted name or legal mark, while conventionally applied to paper, may also be applied to other devices that capture the name or mark.

9. Open system means an environment in which system access is not controlled by persons who are responsible for the content of electronic records that are on the system.

Subpart B—Electronic Records

Sec. 11.10 Controls for closed systems.

Persons who use closed systems to create, modify, maintain, or transmit electronic records shall employ procedures and controls designed to ensure the authenticity, integrity, and, when appropriate, the confidentiality of electronic records, and to ensure that the signer cannot readily repudiate the signed record as not genuine. Such procedures and controls shall include the following:

a) Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.

b) The ability to generate accurate and complete copies of records in both human readable and

electronic form suitable for inspection, review, and copying by the agency. Persons should contact the agency if there are any questions regarding the ability of the agency to perform such review and copying of the electronic records.

c) Protection of records to enable their accurate and ready retrieval throughout the records retention period.

d) Limiting system access to authorized individuals.

e) Use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information. Such audit trail documentation shall be retained for a period at least as long as that required for the subject electronic records and shall be available for agency review and copying.

f) Use of operational system checks to enforce permitted sequencing of steps and events, as appropriate.

g) Use of authority checks to ensure that only authorized individuals can use the system, electronically sign a record, access the operation or computer system input or output device, alter a record, or perform the operation at hand.

h) Use of device (e.g., terminal) checks to determine, as appropriate, the validity of the source of data input or operational instruction.

i) Determination that persons who develop, maintain, or use electronic record/electronic signature systems have the education, training, and experience to perform their assigned tasks.

j) The establishment of, and adherence to, written policies that hold individuals accountable and responsible for actions initiated under their electronic signatures, in order to deter record and signature falsification.

k) Use of appropriate controls over systems documentation including:
   1. Adequate controls over the distribution of, access to, and use of documentation for system operation and maintenance.
   2. Revision and change control procedures to maintain an audit trail that documents time-sequenced development and modification of systems documentation.

Sec. 11.30 Controls for open systems.

Persons who use open systems to create, modify, maintain, or transmit electronic records shall employ procedures and controls designed to ensure the authenticity, integrity, and, as appropriate, the confidentiality of electronic records from the point of their creation to the point of their receipt. Such procedures and controls shall include those identified in Sec. 11.10, as appropriate, and additional measures such as document encryption and use of appropriate digital signature standards to ensure, as necessary under the circumstances, record authenticity, integrity,

and confidentiality.

Sec. 11.50 Signature manifestations.

a) Signed electronic records shall contain information associated with the signing that clearly indicates all of the following:
   1. The printed name of the signer;
   2. The date and time when the signature was executed; and
   3. The meaning (such as review, approval, responsibility, or authorship) associated with the signature.

b) The items identified in paragraphs (a)(1), (a)(2), and (a)(3) of this section shall be subject to the same controls as for electronic records and shall be included as part of any human readable form of the electronic record (such as electronic display or printout).

Sec. 11.70 Signature/record linking.

Electronic signatures and handwritten signatures executed to electronic records shall be linked to their respective electronic records to ensure that the signatures cannot be excised, copied, or otherwise transferred to falsify an electronic record by ordinary means.

Subpart C—Electronic Signatures

Sec. 11.100 General requirements.

a) Each electronic signature shall be unique to one individual and shall not be reused by, or reassigned to, anyone else.

b) Before an organization establishes, assigns, certifies, or otherwise sanctions an individual's electronic signature, or any element of such electronic signature, the organization shall verify the identity of the individual.

c) Persons using electronic signatures shall, prior to or at the time of such use, certify to the agency that the electronic signatures in their system, used on or after August 20, 1997, are intended to be the legally binding equivalent of traditional handwritten signatures.
   1. The certification shall be submitted in paper form and signed with a traditional handwritten signature, to the Office of Regional Operations (HFC-100), 5600 Fishers Lane, Rockville, MD 20857.
   2. Persons using electronic signatures shall, upon agency request, provide additional certification or testimony that a specific electronic signature is the legally binding equivalent of the signer's handwritten signature.

Sec. 11.200 Electronic signature components and controls.

a) Electronic signatures that are not based upon biometrics shall:
   1. Employ at least two distinct identification components such as an identification code and password.
      i. When an individual executes a series of signings during a single, continuous period of controlled system access, the first signing shall be executed using all electronic signature components; subsequent signings shall be executed using at least one electronic signature component that is only executable by, and designed to be used only by, the individual.
      ii. When an individual executes one or more signings not performed during a single, continuous period of controlled system access, each signing shall be executed using all of the electronic signature components.
   2. Be used only by their genuine owners; and
   3. Be administered and executed to ensure that attempted use of an individual's electronic signature by anyone other than its genuine owner requires collaboration of two or more individuals.

b) Electronic signatures based upon biometrics shall be designed to ensure that they cannot be used by anyone other than their genuine owners.

Sec. 11.300 Controls for identification codes/passwords.

Persons who use electronic signatures based upon use of identification codes in combination with passwords shall employ controls to ensure their security and integrity. Such controls shall include:

a) Maintaining the uniqueness of each combined identification code and password, such that no two individuals have the same combination of identification code and password.

b) Ensuring that identification code and password issuances are periodically checked, recalled, or revised (e.g., to cover such events as password aging).

c) Following loss management procedures to electronically deauthorize lost, stolen, missing, or otherwise potentially compromised tokens, cards, and other devices that bear or generate identification code or password information, and to issue temporary or permanent replacements using suitable, rigorous controls.

d) Use of transaction safeguards to prevent unauthorized use of passwords and/or identification codes, and to detect and report in an immediate and urgent manner any attempts at their unauthorized use to the system security unit, and, as appropriate, to organizational management.

e) Initial and periodic testing of devices, such as tokens or cards, that bear or generate identification code or password information to ensure that they function properly and have not been altered in an unauthorized manner.

USA 21CFR New Guidance

Guidance for Industry

Part 11, Electronic Records; Electronic Signatures — Scope and Application

Division of Drug Information, HFD-240

Center for Drug Evaluation and Research (CDER) (Tel) 301-827-4573

http://www.fda.gov/cder/guidance/index.htm

or

Office of Communication, Training and Manufacturers Assistance, HFM-40 Center for Biologics Evaluation and Research (CBER)

http://www.fda.gov/cber/guidelines.htm

Phone: the Voice Information System at 800-835-4709 or 301-827-1800

or

Communications Staff (HFV-12), Center for Veterinary Medicine (CVM) (Tel) 301-594-1755

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U.S. Department of Health and Human Services

Food and Drug Administration

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Center for Veterinary Medicine (CVM)

Office of Regulatory Affairs (ORA)

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Pharmaceutical CGMPs

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Guidance for Industry[1]

Part 11, Electronic Records; Electronic Signatures—Scope and Application

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to describe the Food and Drug Administration's (FDA's) current thinking regarding the scope and application of part 11 of Title 21 of the Code of Federal Regulations; Electronic Records; Electronic Signatures (21 CFR Part 11).[2]

This document provides guidance to persons who, in fulfillment of a requirement in a statute or another part of FDA's regulations to maintain records or submit information to FDA,[3] have chosen to maintain the records or submit designated information electronically and, as a result, have become subject to part 11. Part 11 applies to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted under any records requirements set forth in Agency regulations. Part 11 also applies to electronic records submitted to the Agency under the Federal Food, Drug, and Cosmetic Act (the Act) and the Public Health Service Act (the PHS Act), even if such records are not specifically identified in Agency regulations (§ 11.1). The underlying requirements set forth in the Act, PHS Act, and FDA regulations (other than part 11) are referred to in this guidance document as predicate rules.

As an outgrowth of its current good manufacturing practice (CGMP) initiative for human and animal drugs and biologics,[4] FDA is re-examining part 11 as it applies to all FDA regulated products.

We anticipate initiating rulemaking to change part 11 as a result of that re-examination. This guidance explains that we will narrowly interpret the scope of part 11. While the re-examination of part 11 is under way, we intend to exercise enforcement discretion with respect to certain part 11 requirements. That is, we do not intend to take enforcement action to enforce compliance with the validation, audit trail, record retention, and record copying requirements of part 11 as explained in this guidance. However, records must still be maintained or submitted in accordance with the underlying predicate rules, and the Agency can take regulatory action for noncompliance with such *predicate rules*.

In addition, we intend to exercise enforcement discretion and do not intend to take (or recommend) action to enforce any part 11 requirements with regard to systems that were operational before August 20, 1997, the effective date of part 11 (commonly known as legacy systems) under the circumstances described in section III.C.3 of this guidance.

Note that part 11 remains in effect and that this exercise of enforcement discretion applies only as identified in this guidance.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

In March of 1997, FDA issued final part 11 regulations that provide criteria for acceptance by FDA, under certain circumstances, of electronic records, electronic signatures, and handwritten

signatures executed to electronic records as equivalent to paper records and handwritten signatures executed on paper. These regulations, which apply to all FDA program areas, were intended to permit the widest possible use of electronic technology, compatible with FDA's responsibility to protect the public health.

After part 11 became effective in August 1997, significant discussions ensued among industry, contractors, and the Agency concerning the interpretation and implementation of the regulations. FDA has (1) spoken about part 11 at many conferences and met numerous times with an industry coalition and other interested parties in an effort to hear more about potential part 11 issues; (2) published a compliance policy guide, CPG 7153.17: Enforcement Policy: 21 CFR Part 11; Electronic Records; Electronic Signatures; and (3) published numerous draft guidance documents including the following:

- *21 CFR Part 11; Electronic Records; Electronic Signatures, Validation*
- *21 CFR Part 11; Electronic Records; Electronic Signatures, Glossary of Terms*
- *21 CFR Part 11; Electronic Records; Electronic Signatures, Time Stamps*
- *21 CFR Part 11; Electronic Records; Electronic Signatures, Maintenance of Electronic Records2 1 CFR Part 11; Electronic Records; Electronic Signatures, Electronic Copies of Electronic Records*

Throughout all of these communications, concerns have been raised that some interpretations of the part 11 requirements would (1) unnecessarily restrict the use of electronic technology in a manner that is inconsistent with FDA's stated intent in issuing the rule, (2) significantly increase the costs of compliance to an extent that was not contemplated at the time the rule was drafted, and (3) discourage innovation and technological advances without providing a significant public health benefit. These concerns have been raised particularly in the areas of part 11 requirements for validation, audit trails, record retention, record copying, and legacy systems.

As a result of these concerns, we decided to review the part 11 documents and related issues, particularly in light of the Agency's CGMP initiative. In the *Federal Register* of February 4, 2003 (68 FR 5645), we announced the withdrawal of the draft guidance for industry, 21 CFR Part 11; *Electronic Records; Electronic Signatures, Electronic Copies of Electronic Records*. We had decided we wanted to minimize industry time spent reviewing and commenting on the draft guidance when that draft guidance may no longer represent our approach under the CGMP initiative. Then, in the *Federal Register* of February 25, 2003 (68 FR 8775), we announced the withdrawal of the part 11 draft guidance documents on validation, glossary of terms, time stamps,[5] maintenance of electronic records, and CPG 7153.17. We received valuable public comments on these draft guidances, and we plan to use that information to help with future decision-making with respect to part 11. We do not intend to re-issue these draft guidance documents or the CPG.

We are now re-examining part 11, and we anticipate initiating rulemaking to revise provisions of

that regulation. To avoid unnecessary resource expenditures to comply with part 11 requirements, we are issuing this guidance to describe how we intend to exercise enforcement discretion with regard to certain part 11 requirements during the re-examination of part 11. As mentioned previously, part 11 remains in effect during this re-examination period.

III. DISCUSSION

A. Overall Approach to Part 11 Requirements

As described in more detail below, the approach outlined in this guidance is based on three main elements:

- Part 11 will be interpreted narrowly; we are now clarifying that fewer records will be considered subject to part 11.
- For those records that remain subject to part 11, we intend to exercise enforcement discretion with regard to part 11 requirements for validation, audit trails, record retention, and record copying in the manner described in this guidance and with regard to all part 11 requirements for systems that were operational before the effective date of part 11 (also known as legacy systems).
- We will enforce all predicate rule requirements, including predicate rule record and recordkeeping requirements.

It is important to note that FDA's exercise of enforcement discretion as described in this guidance is limited to specified part 11 requirements (setting aside legacy systems, as to which the extent of enforcement discretion, under certain circumstances, will be more broad). We intend to enforce all other provisions of part 11 including, but not limited to, certain controls for closed systems in § 11.10. For example, we intend to enforce provisions related to the following controls and requirements:

- limiting system access to authorized individuals
- use of operational system checks
- use of authority checks
- use of device checks
- determination that persons who develop, maintain, or use electronic systems have the education, training, and experience to perform their assigned tasks
- establishment of and adherence to written policies that hold individuals accountable for actions initiated under their electronic signatures
- appropriate controls over systems documentation

- controls for open systems corresponding to controls for closed systems bulleted above (§ 11.30)
- requirements related to electronic signatures (e.g., §§ 1 1.50, 1 1.70, 1 1.100, 1 1.200, and 11.300)

We expect continued compliance with these provisions, and we will continue to enforce them. Furthermore, persons must comply with applicable predicate rules, and records that are required to be maintained or submitted must remain secure and reliable in accordance with the predicate rules.

B. Details of Approach – Scope of Part 11

1. Narrow Interpretation of Scope

We understand that there is some confusion about the scope of part 11. Some have understood the scope of part 11 to be very broad. We believe that some of those broad interpretations could lead to unnecessary controls and costs and could discourage innovation and technological advances without providing added benefit to the public health. As a result, we want to clarify that the Agency intends to interpret the scope of part 11 narrowly.

Under the narrow interpretation of the scope of part 11, with respect to records required to be maintained under predicate rules or submitted to FDA, when persons choose to use records in electronic format in place of paper format, part 11 would apply. On the other hand, when persons use computers to generate paper printouts of electronic records, and those paper records meet all the requirements of the applicable predicate rules and persons rely on the paper records to perform their regulated activities, FDA would generally not consider persons to be "using electronic records in lieu of paper records" under §§ 11.2(a) and 11.2(b). In these instances, the use of computer systems in the generation of paper records would not trigger part 11.

2. Definition of Part 11 Records

Under this narrow interpretation, FDA considers part 11 to be applicable to the following records or signatures in electronic format (part 11 records or signatures):

- Records that are required to be maintained under predicate rule requirements and that are maintained in electronic format in place of paper format. On the other hand, records (and any associated signatures) that are not required to be retained under predicate rules, but that are nonetheless maintained in electronic format, are not part 11 records.
- We recommend that you determine, based on the predicate rules, whether specific records are part 11 records. We recommend that you document such decisions.
- Records that are required to be maintained under predicate rules, that are maintained in

electronic format in addition to paper format, and that are relied on to perform regulated activities.

In some cases, actual business practices may dictate whether you are using electronic records instead of paper records under § 11.2(a). For example, if a record is required to be maintained under a predicate rule and you use a computer to generate a paper printout of the electronic records, but you nonetheless rely on the electronic record to perform regulated activities, the Agency may consider you to be using the electronic record instead of the paper record. That is, the Agency may take your business practices into account in determining whether part 11 applies.

Accordingly, we recommend that, for each record required to be maintained under predicate rules, you determine in advance whether you plan to rely on the electronic record or paper record to perform regulated activities. We recommend that you document this decision (e.g., in a Standard Operating Procedure (SOP), or specification document).

- Records submitted to FDA, under predicate rules (even if such records are not specifically identified in Agency regulations) in electronic format (assuming the records have been identified in docket number 92S-02 51 as the types of submissions the Agency accepts in electronic format). However, a record that is not itself submitted, but is used in generating a submission, is not a part 11 record unless it is otherwise required to be maintained under a predicate rule and it is maintained in electronic format.
- Electronic signatures that are intended to be the equivalent of handwritten signatures, initials, and other general signings required by predicate rules. Part 11 signatures include electronic signatures that are used, for example, to document the fact that certain events or actions occurred in accordance with the predicate rule (e.g. approved, reviewed, and verified).

C. Approach to Specific Part 11 Requirements

1. Validation

The Agency intends to exercise enforcement discretion regarding specific part 11 requirements for validation of computerized systems (§ 11.10(a) and corresponding requirements in § 11.30). Although persons must still comply with all applicable predicate rule requirements for validation (e.g., 21 CFR 820.70(i)), this guidance should not be read to impose any additional requirements for validation.

We suggest that your decision to validate computerized systems, and the extent of the validation, take into account the impact the systems have on your ability to meet predicate rule requirements. You should also consider the impact those systems might have on the accuracy, reliability, integrity, availability, and authenticity of required records and signatures. Even if there is no

predicate rule requirement to validate a system, in some instances it may still be important to validate the system.

We recommend that you base your approach on a justified and documented risk assessment and a determination of the potential of the system to affect product quality and safety, and record integrity. For instance, validation would not be important for a word processor used only to generate SOPs.

For further guidance on validation of computerized systems, see FDA's guidance for industry and FDA staff General Principles of Software Validation and also industry guidance such as the GAMP 4 Guide (See References).

2. Audit Trail

The Agency intends to exercise enforcement discretion regarding specific part 11 requirements related to computer-generated, time-stamped audit trails (§ 11.10 (e), (k)(2) and any corresponding requirement in §11.30). Persons must still comply with all applicable predicate rule requirements related to documentation of, for example, date (e.g., § 58.130(e)), time, or sequencing of events, as well as any requirements for ensuring that changes to records do not obscure previous entries.

Even if there are no predicate rule requirements to document, for example, date, time, or sequence of events in a particular instance, it may nonetheless be important to have audit trails or other physical, logical, or procedural security measures in place to ensure the trustworthiness and reliability of the records.[6] We recommend that you base your decision on whether to apply audit trails, or other appropriate measures, on the need to comply with predicate rule requirements, a justified and documented risk assessment, and a determination of the potential effect on product quality and safety and record integrity. We suggest that you apply appropriate controls based on such an assessment. Audit trails can be particularly appropriate when users are expected to create, modify, or delete regulated records during normal operation.

3. Legacy Systems[7]

The Agency intends to exercise enforcement discretion with respect to all part 11 requirements for systems that otherwise were operational prior to August 20, 1997, the effective date of part 11, under the circumstances specified below.

This means that the Agency does not intend to take enforcement action to enforce compliance with any part 11 requirements if all the following criteria are met for a specific system:

- The system was operational before the effective date.
- The system met all applicable predicate rule requirements before the effective date.
- The system currently meets all applicable predicate rule requirements.

- You have documented evidence and justification that the system is fit for its intended use (including having an acceptable level of record security and integrity, if applicable).

If a system has been changed since August 20, 1997, and if the changes would prevent the system from meeting predicate rule requirements, Part 11 controls should be applied to Part 11 records and signatures pursuant to the enforcement policy expressed in this guidance.

4. Copies of Records

The Agency intends to exercise enforcement discretion with regard to specific part 11 requirements for generating copies of records (§ 11.10 (b) and any corresponding requirement in §11.30). You should provide an investigator with reasonable and useful access to records during an inspection. All records held by you are subject to inspection in accordance with predicate rules (e.g., §§ 211.180(c), (d), and 108.35(c)(3)(ii)).

We recommend that you supply copies of electronic records by:

- Producing copies of records held in common portable formats when records are maintained in these formats
- Using established automated conversion or export methods, where available, to make copies in a more common format (examples of such formats include, but are not limited to, PDF, XML, or SGML)

In each case, we recommend that the copying process used produces copies that preserve the content and meaning of the record. If you have the ability to search, sort, or trend part 11 records, copies given to the Agency should provide the same capability if it is reasonable and technically feasible. You should allow inspection, review, and copying of records in a human readable form at your site using your hardware and following your established procedures and techniques for accessing records.

5. Record Retention

The Agency intends to exercise enforcement discretion with regard to the part 11 requirements for the protection of records to enable their accurate and ready retrieval throughout the records retention period (§ 11.10 (c) and any corresponding requirement in §11.30).

Persons must still comply with all applicable predicate rule requirements for record retention and availability (e.g., §§ 21 1.180(c),(d), 108.25(g), and 108.35(h)).

We suggest that your decision on how to maintain records be based on predicate rule requirements and that you base your decision on a justified and documented risk assessment and a determination of the value of the records over time.

FDA does not intend to object if you decide to archive required records in electronic format to nonelectronic media such as microfilm, microfiche, and paper, or to a standard electronic file format (examples of such formats include, but are not limited to, PDF, XML, or SGML). Persons must still comply with all predicate rule requirements, and the records themselves and any copies of the required records should preserve their content and meaning. As long as predicate rule requirements are fully satisfied and the content and meaning of the records are preserved and archived, you can delete the electronic version of the records. In addition, paper and electronic record and signature components can co-exist (i.e., a hybrid[8] situation) as long as predicate rule requirements are met and the content and meaning of those records are preserved.

IV. REFERENCES

Food and Drug Administration References

1. Glossary of Computerized System and Software Development Terminology (Division of Field Investigations, Office of Regional Operations, Office of Regulatory Affairs, FDA 1995) (http: //www.fda.gov/ora/inspect_ref/igs/gloss.html)

2. General Principles of Software Validation; Final Guidance for Industry and FDA Staff (FDA, Center for Devices and Radiological Health, Center for Biologics Evaluation and Research, 2002) (http: //www.fda.gov/cdrh/comp/guidance/938.html)

3. Guidance for Industry, FDA Reviewers, and Compliance on Off-The-Shelf Software Use in Medical Devices (FDA, Center for Devices and Radiological Health, 1999) (http://www.fda.gov/cdrh/ode/ guidance/585.html)

4. Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach; A Science and Risk-Based Approach to Product Quality Regulation Incorporating an Integrated Quality Systems Approach (FDA 2002) (http ://www.fda.gov/oc/guidance/gmp .html)

Industry References

1. The Good Automated Manufacturing Practice (GAMP) Guide for Validation of Automated Systems, GAMP 4 (ISPE/GAMP Forum, 2001) (http://www.ispe.org/gamp/)

2. ISO/IEC 17799:2000 (BS 7799:2000) Information technology – Code of practice for information security management (ISO/IEC, 2000)

3. ISO 14971:2002 Medical Devices- Application of risk management to medical devices (ISO, 2001)

Endnotes

1. This guidance has been prepared by the Office of Compliance in the Center for Drug Evaluation and Research (CDER) in consultation with the other Agency centers and the Office of Regulatory Affairs at the Food and Drug Administration.

2. 62 FR 13430

3. These requirements include, for example, certain provisions of the Current Good Manufacturing Practice regulations (21 CFR Part 211), the Quality System regulation (21 CFR Part 820), and the Good Laboratory Practice for Nonclinical Laboratory Studies regulations (21 CFR Part 58).

4. See Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach; A Science and Risk-Based Approach to Product Quality Regulation Incorporating an Integrated Quality Systems Approach at www.fda.gov/oc/guidance/gmp.html.

5. Although we withdrew the draft guidance on time stamps, our current thinking has not changed in that when using time stamps for systems that span different time zones, we do not expect you to record the signer's local time. When using time stamps, they should be implemented with a clear understanding of the time zone reference used. In such instances, system documentation should explain time zone references as well as zone acronyms or other naming conventions.

6. Various guidance documents on information security are available (see References).

7. In this guidance document, we use the term legacy system to describe systems already in operation before the effective date of part 11.

8. Examples of hybrid situations include combinations of paper records (or other nonelectronic media) and electronic records, paper records and electronic signatures, or handwritten signatures executed to electronic records.

USA FDA Compliance Program Guidance Manual Program

Chapter 48—Bioresearch Monitoring

PART III – INSPECTIONAL

A. General Instructions

1. The investigator will determine the current state of GLP compliance by evaluating the laboratory facilities, operations, and study performance as outlined in Parts III, C, and D of this program.

1. Organization Chart—If the facility maintains an organization chart, obtain a current version of the chart for use during the inspection and submit it in the EIR.
2. Facility Floor-plan Diagram—Obtain a diagram of the facility. The diagram may identify areas that are not used for GLP activities. If it does not, request that appropriate facility personnel identify any areas that are not used for GLP activities. Use during the inspection and submit it in the EIR.
3. Master Schedule Sheet—Obtain a copy of the firm's master schedule sheet for all studies listed since the last GLP inspection or last two years and select studies as defined in 21 CFR 58.3(d). If the inspection is the first inspection of the facility, review the entire master schedule. If studies are identified as non-GLP, determine the nature of several studies to verify the accuracy of this designation. See 21 CFR 58.1 and 58.3(d). In contract laboratories determine who decides if a study is a GLP study.
4. Identification of Studies
   a. Directed Inspections—Inspection assignments will identify studies to be audited.
   b. Surveillance inspections—Inspection assignments may identify one or more studies to be audited. If the assignment does not identify a study for coverage, or if the referenced study is not suitable to assess all portions of current GLP compliance, the investigator will select studies as necessary to evaluate all areas of laboratory operations. When additional studies are selected, first priority should be given to FDA studies for submission to the assigning Center. NOTE: Studies performed for submission to other government agencies, e.g., Environmental Protection Agency, National Toxicology Program, National Cancer Institute, etc., will not be audited without authorization from the Bioresearch Monitoring Program Coordinator (HFC-230). However, this authorization is not necessary to briefly look at one of these studies to assess the ongoing operations of a portion of the facility.

      1. Criteria for selecting on-going and completed studies

      a) Safety studies conducted on FDA-regulated products that have been initiated or completed since the last GLP inspection.

b) Safety studies that encompass the full scope of laboratory operations.

c) Studies that are significant to safety assessment, e.g. carcinogenicity, reproductive toxicity, chronic toxicity studies.

d) Studies in several species of animals.

The investigator is encouraged to contact the Center for guidance on study selection.

2. Ongoing Studies—Obtain a copy of the study protocol and determine the schedule of activities that will be underway during the inspection. This information should be used to schedule inspections of on-going laboratory operations, as well as equipment and facilities associated with the study. If there are no activities underway in a given area for the study selected, evaluate the area based on ongoing activities.
3. Completed Studies—The data audit should be carried out as outlined in Part III, D. If possible, accompany laboratory personnel when they retrieve the study data to assess the adequacy of data retention, storage, and retrieval as described in Part III, C 10.

B. Areas of Expertise of the Facility

Testing facilities may conduct one or more types of studies within the scope of GLP regulations. The field investigator should identify in the EIR the types of studies conducted at the facility using the following broad categories:

1. Physical-chemical testing
2. Toxicity studies
3. Mutagenicity studies
4. Tissue residue depletion studies
5. Analytical and clinical chemistry testing
6. Other studies (specify)

C. Establishment Inspections

The facility inspection should be guided by the GLP regulations. The following areas should be evaluated and described as appropriate.

1. Organization and Personnel (21 CFR 58.29, 58.31, 58.33)

a. Purpose: To determine whether the organizational structure is appropriate to ensure that studies are conducted in compliance with GLP regulations, and to determine whether management, study directors, and laboratory personnel are fulfilling their responsibilities under the GLPs.

b. Management Responsibilities (21 CFR 58.31) —Identify the various organizational units,

their role in carrying out GLP study activities, and the management responsible for these organizational units. This includes identifying personnel who are performing duties at locations other than the test facility and identifying their line of authority. If the facility has an organization chart, much of this information can be determined from the chart.

Determine if management has procedures for assuring that the responsibilities in 58.31 can be carried out. Look for evidence of management involvement, or lack thereof, in the following areas:

1. Assigning and replacing study directors.
2. Control of study director workload (use the Master Schedule to assess workload).
3. Establishment and support of the Quality Assurance Unit (QAU), including assuring that deficiencies reported by the QAU are communicated to the study directors and acted upon.
4. Assuring that test and control articles or mixtures are appropriately tested for identity, strength, purity, stability, and uniformity.
5. Assuring that all study personnel are informed of and follow any special test and control article handling and storage procedures.
6. Providing required study personnel, resources, facilities, equipment, and materials.
7. Reviewing and approving protocols and standard operating procedures (SOPs).
8. Providing GLP or appropriate technical training.

c. Personnel (21 CFR 58.29) - Identify key laboratory and management personnel, including any consultants or contractors used, and review personnel records, policies, and operations to determine if:

1. Summaries of training and position descriptions are maintained and are current for selected employees.
2. Personnel have been adequately trained to carry out the study functions that they perform.
3. Personnel have been trained in GLPs.
4. Practices are in place to ensure that employees take necessary health precautions, wear appropriate clothing, and report illnesses to avoid contamination of the test and control articles and test systems.

If the firm has computerized operations, determine the following (See also attachment A):

a. Who was involved in the design, development, and validation of the computer system?
b. Who is responsible for the operation of the computer system, including inputs, processing, and output of data?
c. Whether computer system personnel have training commensurate with their responsibilities, including professional training and training in GLPs?
d. Whether some computer system personnel are contractors who are present on-

site full-time, or nearly full-time. The investigation should include these contractors as though they were employees of the firm. Specific inquiry may be needed to identify these contractors, as they may not appear on organization charts.

e. Interview and observe personnel using the computerized systems to assess their training and performance of assigned duties.

d. Study director (21 CFR 58.33)

1. Assess the extent of the study director's actual involvement and participation in the study. In those instances when the study director is located off-site, review any correspondence/records between the testing facility management and quality assurance unit and the off-site study director. Determine that the study director is being kept immediately apprised of any problems that may affect the quality and integrity of the study.
2. Assess the procedures by which the study director:
    a. Assures the protocol and any amendments have been properly approved and are followed.
    b. Assures that all data are accurately recorded and verified.
    c. Assures that data are collected according to the protocol and SOPs.
    d. Documents unforeseen circumstances that may affect the quality and integrity of the study and implements corrective action.
    e. Assures that study personnel are familiar with and adhere to the study protocol and SOPs.
    f. Assures that study data are transferred to the archives at the close of the study.

e. EIR Documentation and Reporting—Collect exhibits to document deficiencies. This may include SOPs, organizational charts, position descriptions, and CVs, as well as study-related memos, records, and reports for the studies selected for review. The use of outside or contract facilities must be noted in the EIR. The assigning Center should be contacted for guidance on inspection of these facilities.

2. Quality Assurance Unit (QAU; 21 CFR 58.35)

a. Purpose: To determine if the test facility has an effective, independent QAU that monitors significant study events and facility operations, reviews records and reports, and assures management of GLP compliance.

b. QAU Operations - (21 CFR 58.35(b-d)) — Review QAU SOPs to assure that they cover all methods and procedures for carrying out the required QAU functions, and confirm that they are being followed. Verify that SOPs exist and are being followed for QAU activities including, but not limited to, the following:

1. Maintenance of a master schedule sheet.

2. Maintenance of copies of all protocols and amendments.
3. Scheduling of its in-process inspections and audits.
4. Inspection of each nonclinical laboratory study at intervals adequate to assure the integrity of the study, and maintenance of records of each inspection.
5. Immediately notify the study director and management of any problems that are likely to affect the integrity of the study.
6. Submission of periodic status reports on each study to the study director and management.
7. Review of the final study report.
8. Preparation of a statement to be included in the final report that specifies the dates inspections were made and findings reported to management and to the study director.
9. Inspection of computer operations.

Verify that, for any given study, the QAU is entirely separate from and independent of the personnel engaged in the conduct and direction of that study. Evaluate the time QAU personnel spend in performing in-process inspection and final report audits. Determine if the time spent is sufficient to detect problems in critical study phases and if there are adequate personnel to perform the required functions.

NOTE: The investigator may request the firm's management to certify in writing that inspections are being implemented, performed, documented, and followed-up in accordance with this section (See 58.35(d)).

c. EIR Documentation and Reporting — Obtain a copy of the master schedule sheet dating from the last routine GLP inspection or covering the past two years. If the master schedule is too voluminous, obtain representative pages to permit headquarters review. When master schedule entries are coded, obtain the code key. Deficiencies should be fully reported and documented in the EIR. Documentation to support deviations may include copies of QAU SOPs, list of QAU personnel, their curriculum vitae (CVs) or position descriptions, study-related records, protocols, and final reports.

3. Facilities (21 CFR 58.41 - 51)

a. Purpose: Assess whether the facilities are of adequate size and design.

b. Facility Inspection
    1. Review environmental controls and monitoring procedures for critical areas (i.e., animal rooms, test article storage areas, laboratory areas, handling of bio-hazardous material, etc.) and determine if they appear adequate and are being followed.
    2. Review the SOPs that identify materials used for cleaning critical areas and equipment, and assess the facility's current cleanliness.

3. Determine whether there are appropriate areas for the receipt, storage, mixing, and handling of the test and control articles.
4. Determine whether separation is maintained in rooms where two or more functions requiring separation are performed.
5. Determine that computerized operations and archived computer data are housed under appropriate environmental conditions (e.g., protected from heat, water, and electromagnetic forces).

c. EIR Documentation and Reporting - Identify which facilities, operations, SOPs, etc., were inspected. Only significant changes in the facility from previous inspections need be described. Facility floor plans may be collected to illustrate problems or changes. Document any conditions that would lead to contamination of test articles or to unusual stress of test systems.

4. Equipment (21 CFR 58.61 - 63)

a. Purpose: To assess whether equipment is appropriately designed and of adequate capacity and is maintained and operated in a manner that ensures valid results.

b. Equipment Inspection - Assess the following:
   1. The general condition, cleanliness, and ease of maintenance of equipment in various parts of the facility.
   2. The heating, ventilation, and air conditioning system design and maintenance, including documentation of filter changes and temperature/humidity monitoring in critical areas.
   3. Whether equipment is located where it is used and that it is located in a controlled environment, when required.
   4. Non-dedicated equipment for preparation of test and control article carrier mixtures is cleaned and decontaminated to prevent cross contamination.
   5. For representative pieces of equipment check the availability of the following:
      a. SOPS and/or operating manuals.
      b. Maintenance schedule and log.
      c. Standardization/calibration procedure, schedule, and log.
      d. Standards used for calibration and standardization.
   6. For computer systems, assess that the following procedures exist and are documented (See also attachment A):
      a. Validation study, including validation plan and documentation of the plan's completion.
      b. Maintenance of equipment, including storage capacity and back-up procedures.
      c. Control measures over changes made to the computer system, which include the evaluation of the change, necessary test design, test data, and final acceptance of the change.

d. Evaluation of test data to assure that data are accurately transmitted and handled properly when analytical equipment is directly interfaced to the computer.

e. Procedures for emergency back-up of the computer system (e.g., back-up battery system and data forms for recording data in the event of a computer failure or power outage).

c. EIR Documentation and Reporting - The EIR should list which equipment, records, and procedures were inspected and the studies to which they are related. Detail any deficiencies that might result in contamination of test articles, uncontrolled stress to test systems, and/or erroneous test results.

5. Testing Facility Operations (21 CFR 58.81)

a. Purpose: To determine if the facility has established and follows written SOPs necessary to carry out study operations in a manner designed to ensure the quality and integrity of the data.

b. SOP Evaluation

1. Review the SOP index and representative samples of SOPs to ensure that written procedures exist to cover at least all of the areas identified in 58.8 1(b).
2. Verify that only current SOPs are available at the personnel workstations.
3. Review key SOPs in detail and check for proper authorization signatures and dates, and general adequacy with respect to the content (i.e., SOPs are clear, complete, and can be followed by a trained individual).
4. Verify that changes to SOPs are properly authorized and dated and that a historical file of SOPs is maintained.
5. Ensure that there are procedures for familiarizing employees with SOPs.
6. Determine that there are SOPs to ensure the quality and integrity of data, including input (data checking and verification), output (data control), and an audit trail covering all data changes.
7. Verify that a historical file of outdated or modified computer programs is maintained. If the firm does not maintain old programs in digital form, ensure that a hard copy of all programs has been made and stored.
8. Verify that SOPs are periodically reviewed for current applicability and that they are representative of the actual procedures in use.
9. Review selected SOPs and observe employees performing the operation to evaluate SOP adherence and familiarity.

c. EIR Documentation and Reporting—Submit SOPs, data collection forms, and raw data records as exhibits that are necessary to support and illustrate deficiencies.

6. Reagents and Solutions (21 CFR 58.83)

a. Purpose: To determine that the facility ensures the quality of reagents at the time of receipt and subsequent use.

1. Review the procedures used to purchase, receive, label, and determine the acceptability of reagents and solutions for use in the studies.
2. Verify that reagents and solutions are labeled to indicate identity, titer or concentration, storage requirements, and expiration date.
3. Verify that for automated analytical equipment, the profile data accompanying each batch of control reagents are used.
4. Check that storage requirements are being followed.

7. Animal Care (21 CFR 58.90)

a. Purpose: To assess whether animal care and housing is adequate to minimize stress and uncontrolled influences that could alter the response of test system to the test article.

b. Inspect the animal room(s) housing the study to observe operations, protocol and SOP adherence, and study records. Refer to IOM 145.2 prior to inspecting sub-human primate facilities.

1. Determine that there are adequate SOPs covering environment, housing, feeding, handling, and care of laboratory animals, and that the SOPs and the protocol instructions are being followed.
2. Review pest-control procedures and documentation of the chemicals used. Identify individuals responsible for the program. When a contractor provides the pest control, determine if someone from the laboratory accompanies the exterminator at all times.
3. Determine whether the facility has an Institutional Animal Care and Use Committee (IACUC). Obtain and submit a copy of the Committee's Standard Operating Procedures and the most recent committee minutes to verify committee operation.
4. Determine that all newly received animals are appropriately isolated, identified, and their health status is evaluated.
5. Verify that treatment given to animals that become diseased is authorized by the study director and documented.
6. For a representative sample of animals, compare individual animal identification against corresponding housing unit identification and dose group designations to assure that animals are appropriately identified.
7. For a representative sample of animals, review daily observation logs and verify their accuracy for animals reported as dead or having external gross lesions or masses.
8. Ensure that animals of different species, or animals of the same species on different projects, are separated as necessary.
9. Verify that cages, racks, and accessory equipment are cleaned and sanitized, and that appropriate bedding is used.

10. Determine that feed and water samples are collected at appropriate sources, analyzed periodically, and that analytical documentation is maintained.

c. EIR Documentation and Reporting - The EIR should identify which areas, operations, SOPs, studies, etc., were inspected and document any deficiencies.

8. Test and Control Articles (21 CFR 58.105 - 113)

a. Purpose: To determine that procedures exist to assure that test and control articles and mixtures of articles with carriers meet protocol specifications throughout the course of the study, and that accountability is maintained.

b. Characterization and Stability of Test Articles (21 CFR 58.105) - The responsibility for carrying out appropriate characterization and stability testing may be assumed by the facility performing the study or by the study sponsor. **When test article characterization and stability testing is performed by the sponsor, verify that the test facility has received documentation that this testing has been conducted.**

1. Verify that procedures are in place to ensure that:
    a. The acquisition, receipt and storage of test articles, and means used to prevent deterioration and contamination are as specified.
    b. The identity, strength, purity, and composition, (i.e., characterization) to define the test and control articles are determined for each batch and are documented.
    c. The stability of test and control articles is documented.
    d. The transfer of samples from the point of collection to the analytical laboratory is documented.
    e. Storage containers are appropriately labeled and assigned for the duration of the study.
    f. Reserve samples of test and control articles for each batch are retained for studies lasting more than four weeks.

c. Test and Control Article Handling (21 CFR 58.107)

1. Determine that there are adequate procedures for:
    a. Documentation for receipt and distribution.
    b. Proper identification and storage.
    c. Precluding contamination, deterioration, or damage during distribution.
2. Inspect test and control article storage areas to verify that environmental controls, container labeling, and storage are adequate.
3. Observe test and control article handling and identification during the distribution and administration to the test system.
4. Review a representative sample of accountability records and, if possible, verify their accuracy by comparing actual amounts in the inventory. For completed studies verify documentation of final test and control article reconciliation.

d. Mixtures of Articles with Carriers (58.113) - If possible, observe the preparation, sampling, testing, storage, and administration of mixtures. Verify that analytical tests are conducted, as appropriate, to:

1. Determine uniformity of mixtures and to determine periodically the concentration of the test or control article in the mixture, and
2. Determine the stability as required under study conditions.

Verify that the results are reported to the study director. When the sponsor performs analytical testing, concentration data may be reported to the study director as absolute or relative (percent of theoretical) values.

e. EIR Documentation and Reporting - Identify the test articles, SOPs, facilities, equipment, operations, etc., inspected. Review the analytical raw data versus the reported results for accuracy of reporting and overall integrity of the data that is being collected. Where deficiencies or other information suggest a problem with the purity, identity, strength, etc., of the test article or the concentration of test article mixtures, document and obtain copies of the analytical raw data and any related reports.

Consideration should be given to collecting a sample as described in Part III, G.

9. Protocol and Conduct of Nonclinical Laboratory Study (21 CFR 58.120 - 130)

a Purpose: To determine if study protocols are properly written and authorized, and that studies are conducted in accordance with the protocol and SOPs.

b. Study Protocol (21 CFR 58.120)

1. Review SOPs for protocol preparation and approval and verify they are followed.
2. Review the protocol to determine if it contains required elements.
3. Review all changes, revisions, or amendments to the protocol to ensure that they are authorized, signed, and dated by the study director.
4. Verify that all copies of the approved protocol contain all changes, revisions, or amendments.

c. Conduct of the Nonclinical Laboratory Study (21 CFR 58.130) —Evaluate the following laboratory operations, facilities, and equipment to verify conformity with protocol and SOP requirements for:

1. Test system monitoring.
2. Recording of raw data (manual and automated).
3. Corrections to raw data (corrections must not obscure the original entry and must be dated, initialed, and explained).
4. Randomization of test systems.
5. Collection and identification of specimens.
6. Authorized access to data and computerized systems.

d. EIR Reporting and Documentation—Identify the study(ies) inspected and, if available, the associated FDA research or marketing permit numbers. Report and document any deficiencies observed. Submit, as exhibits, a copy of all protocols and amendments that were reviewed.

10. Records and Reports (21 CFR 58.185 - 195)

a. Purpose: To assess how the test facility stores and retrieves raw data, documentation, protocols, final reports, and specimens.

b. Reporting of Study Results (21 CFR 58.185)—Determine if the facility prepares a final report for each study conducted. For selected studies, obtain the final report, and verify that it contains the following:

1. The required elements in 21 CFR 58.185(a)(1-14), including the identity (name and address) of any subcontractor facilities and portion of the study contracted, and a description of any computer program changes.
2. Dated signature of the study director (21 CFR 58.185(b)).
3. Corrections or additions to the final report are made in compliance with 21 CFR 58.185(c).

c. Storage and Retrieval of Records and Data (21 CFR 58.190)

1. Verify that raw data, documentation, protocols, final reports, and specimens have been retained.
2. Identify the individual responsible for the archives. Determine if delegation of duties to other individuals in maintaining the archives has occurred.
3. Verify that archived material retained or referred to in the archives is indexed to permit expedient retrieval. It is not necessary that all data and specimens be in the same archive location. For raw data and specimens retained elsewhere, the archives index must make specific reference to those other locations.
4. Verify that access to the archives is controlled and determine that environmental controls minimize deterioration.
5. Ensure that there are controlled procedures for adding or removing material. Review archive records for the removal and return of data and specimens. Check for unexplained or prolonged removals.
6. Determine how and where computer data and backup copies are stored, that records are indexed in a way to allow access to data stored on electronic media, and that environmental conditions minimize deterioration.
7. Determine to what electronic media such as tape cassettes or ultra high capacity portable discs the test facility has the capacity of copying records in electronic form. Report names and identifying numbers of both copying equipment type and electronic medium type to enable agency personnel to bring electronic media to future inspections for

collecting exhibits.

d. EIR Documentation and Reporting—Provide a brief summary of the facility's report preparation procedures and their retention and retrieval of records, reports, and specimens. If records are archived off-site, obtain a copy of documentation of the records which were transferred and where they are located. Describe and document deficiencies.

D. Data Audit

In addition to the procedures outlined above for evaluating the overall GLP compliance of a firm, the inspection should include the audit of at least one completed study. Studies for audit may be assigned by the Center or selected by the investigator as described in Part III, A. The audit will include a comparison of the protocol (including amendments to the protocol), raw data, records, and specimens against the final report to substantiate that protocol requirements were met and that findings were fully and accurately reported.

1. For each study audited, the study records should be reviewed for quality to ensure that data are:
    a. Attributable—the raw data can be traced, by signature or initials and date to the individual observing and recording the data. Should more than one individual observe or record the data, that fact should be reflected in the data.
    b. Legible—the raw data are readable and recorded in a permanent medium. If changes are made to original entries, the changes:
        1. Must not obscure the original entry.
        2. Indicate the reason for change.
        3. Must be signed or initialed and dated by the person making the change.
    c. Contemporaneous—the raw data are recorded at the time of the observation.
    d. Original—the first recording of the data.
    e. Accurate—the raw data are true and complete observations. For data entry forms that require the same data to be entered repeatedly, all fields should be completed or a written explanation for any empty fields should be retained with the study records.
2. General
    a. Determine if there were any significant changes in the facilities, operations, and QAU functions other than those previously reported.
    b. Determine whether the equipment used was inspected, standardized, and calibrated prior to, during, and after use in the study. If equipment malfunctioned, review the remedial action, and ensure that the final report addresses whether the malfunction affected the study.
    c. Determine if approved SOPs existed during the conduct of the study.
    d. Compare the content of the protocol with the requirements in 21 CFR 58.120.
    e. Review the final report for the study director's dated signature and the QAU statement

as required in 21 CFR 58.35(b)(7).

3. Protocol vs. Final Report—Study methods described in the final report should be compared against the protocol and the SOPs to confirm those requirements were met. Examples include, but are not limited to, the following:
    a. Selection and acquisition of the test system, i.e., species, source, weight range, number, age, date ordered, date received.
    b. Procedure for receipt, examination, and isolation of newly received animals.
    c. Methods of test system identification, housing, and assignment to study.
    d. Types and occurrences of diseases and clinical observations prior to and during the study, as well as any treatments administered.
    e. Frequency and methods of sampling and analysis for contaminants in feed and water.
    f. Feed and water contaminant levels did not exceed limits specified in the protocol.
    g. Types of bedding and pest control materials do not interfere with the study.
    h. Preparation and administration of test and/or control articles.
    i. Analysis of test article/test article carrier mixtures.
    j. Observation of the test system response to test article.
    k. Handling of dead or moribund animals.
    l. Collection and analysis of specimens and raw data.
    m. Necropsy, gross pathology, and histopathology.

4. Final Report vs. Raw Data
    a. The audit should include a detailed review of records, memorandum, and other raw data to confirm that the findings in the final report completely and accurately reflect the raw data. Representative samples of raw data should be audited against the final report. Examples of types of data to be checked include, but are not limited to, the following:
        1. Animal body weight records.
        2. Food and water consumption records.
        3. Test system observation and dosing records.
        4. Records for the analysis of uniformity, concentration, and stability of test and control article mixtures.
        5. Protocol-required analyses (e.g., urinalysis, hematology, blood chemistry, ophthalmologic exams).
        6. Necropsy and gross pathology records.
        7. Histopathology, including records for tissue processing and slide preparation.
        8. Conformity between "interim" reports (e.g., a report on the first year of a multi-year study) and the final report.
    b. A representative number of animals from selected dose groups (initially the control and high)

should be traced from receipt through final histopathologic examination. Evaluate for the following:

1. The accuracy of individual test system identification.
2. Review trends in each parameter measured or observed and note inconsistencies.
3. Explanations for reported data outliers.
4. Conformity between in vivo test system observations and gross pathology observations.
5. Conformity between gross pathology observations and histopathologic examinations.
6. Documentation of unforeseen circumstances that may have affected the quality and integrity of the study.

5. Specimens vs. Final Report—The audit should include examination of a representative sample of specimens in the archives for confirmation of the number and identity of specimens in the final report.
6. EIR Documentation and Reporting
   a. All studies audited should be identified by:
      1. Sponsor's name.
      2. Study title (and any study numbers).
      3. Study director's name.
      4. Test article name and/or code.
      5. Test system.
      6. The date the protocol was signed by the study director.
      7. In-life starting and ending dates.
      8. The date the study director signed the final report. and if available,
      9. The FDA research or marketing application number.
   b. Describe and document any significant deficiencies in the conduct or reporting of the study. Obtain a copy of the narrative study report and protocol.

E. Refusal to Permit Inspection

Field investigators should refer to IOM Section 514 for general guidance on dealing with refusal to permit inspection. Test facility management should be advised that the agency will not consider a nonclinical laboratory study in support of a research or marketing permit if the testing facility refuses to permit inspection (58.15(b)).

REFUSAL TO PERMIT INSPECTION OF FACILITIES OR STUDIES SHOULD BE REPORTED IMMEDIATELY BY TELEPHONE TO THE BIORESEARCH MONITORING PROGRAM COORDINATOR (HFC-230), (301- 827-0425), AND FOLLOWED-UP BY FAX TO HFC-230 (30 1-827-0482) WITH AN INFORMATION COPY TO THE ASSIGNING CENTER.

Under this program, partial refusals, including refusal to permit access to, and copying of the master schedule (including any code sheets), SOPs, and other documents pertaining to the inspection will be treated as a "total" refusal to permit inspection.

F. Sealing of Research Records

Whenever a field investigator encounters questionable or suspicious records under any Bioresearch Monitoring Program, and is unable to copy or review them immediately, and has reason for preserving the integrity of those records, **the investigator is to immediately contact by telephone HFC-230 for instructions.** Refer to IOM 453.7 for more information.

G. Samples

1. Collection of samples should be considered when the situation under audit or surveillance suggests that the facility had, or is having, problems in the area of characterization, stability, storage, contamination, or dosage preparation. **The investigator should contact the assigning Center and the Division of Field Science (HFC-140) before samples are collected**. If the field investigator collects a sample, a copy of the methodology and reference samples from the sponsor or the testing facility must also be **obtained**. The copy will be sent to HFC- 140 for designation of a laboratory to perform the sample analysis according to instrument capabilities and the availability of the selected district laboratory. The investigator should contact HFC- 140 at (301) 827-7605 for specific disposition/handling instructions. The investigator must use the appropriate 7-digit code for product collected and provide complete documentation with each sample for possible legal/administrative actions.
2. Samples may include physical samples of:
    a. Carrier.
    b. Test article.
    c. Control article.
    d. Mixtures of test or control articles with carriers.
    e. Specimens including wet tissues, tissue blocks, and slides (see above regarding Center and HFC-140 authorization and instructions).

H. Inspectional Observations

A FDA 483 listing inspectional observations will be issued under this program. Findings should not be listed on the FDA 483 if in the opinion of the field investigator:

1. The findings are problems that have been observed and corrected by the firm through its internal procedures.
2. The findings are minor and are one-time occurrences that have no impact on the firm's operations, study conduct, or data integrity.

Findings that are not considered significant enough to be listed on the FDA 483 may be discussed with the firm's management. Such discussions must be reported in the EIR.

I. Establishment Inspection Reports

Because the Centers are solely responsible for issuing post-inspection correspondence, each EIR must include the full name, title, academic degree(s), and mailing address of the most responsible person at the test facility (For universities the most responsible person would typically be a member of the administration (e.g., department chair, dean)).

Documentation necessary to support the observations listed on the FDA 483 should be collected, submitted, and referenced in the EIR narrative. Suspected violations under Title 21 must be documented sufficiently to form the basis for legal or administrative action. Discuss potential violations under Title 18 with your supervisor and District compliance officer prior to extensive documentation.

1. Full Reporting

   A full report will be prepared and submitted in the following situations:

   a. The initial GLP inspection of a facility.
   b. All inspections that may result in an OAI classification.
   c. Any assignment specifically requesting a full report.

   The EIR should contain the headings described in IOM 593.3, in addition to the headings outlined in Part III, C, and D. The report must always include sufficient information and documentation to support the recommended classification.

2. Abbreviated Reporting
   a. Field investigators may use abbreviated reporting for the following types of assignments:
      1. Surveillance inspections (except for initial inspections) of a facility when it is apparent from the findings that the inspection may result in a final classification of NAI or VAI. These reports must include enough documented information to support the final classification.
      2. Directed inspections and data audits provided the report fully covers all aspects of the specific topic of the inspection (i.e., operations, past deficiencies, assigned studies, etc.) and documents significant adverse findings to support the final classification.

   b. Format
      1. The EIR should be clearly identified as an abbreviated report.
      2. The report should include all the headings described in IOM section 593.1 and include:
         a. The identity of the studies selected for audit and review
         b. Identification of the areas, operations, and amount of data that were inspected

(e.g., identity and percent of records reviewed in a specific area, number of animals tracked, percent of slides checked for accountability, etc.)

c. All adverse observations will be fully discussed in the EIR and documented to permit assessment of their impact on the quality and integrity of the studies.

If the Center review reveals that an abbreviated report is inadequate, the Center will notify HFC-130 that additional information is required.

ATTACHMENT A

Computerized Systems

The intent of this attachment is to collect, in one place, references to computer systems found throughout Part III. Computer systems and operations should be thoroughly covered during inspection of any facility. No additional reporting is required under this Attachment.

In August 1997, the Agency's regulation on electronic signatures and electronic recordkeeping became effective. The Regulation, at 21 CFR Part 11, describes the technical and procedural requirements that must be met if a firm chooses to maintain records electronically and/or use electronic signatures. Part 11 works in conjunction with other FDA regulations and laws that require recordkeeping. Those regulations and laws ("predicate rules') establish requirements for record content, signing, and retention.

Certain older electronic systems may not have been in full compliance with Part 11 by August 1997 and modification to these so called "legacy systems" may take more time. Part 11 does not grandfather legacy systems and FDA expects that firms using legacy systems are taking steps to achieve full compliance with Part 11.

If a firm is keeping electronic records or using electronic signatures, determine if they are in compliance with 21 CFR Part 11. Determine the depth of part 11 coverage on a case by case basis, in light of initial findings and program resources. At a minimum ensure that: (1) the firm has prepared a corrective action plan for achieving full compliance with part 11 requirements, and is making progress toward completing that plan in a timely manner; (2) accurate and complete electronic and human readable copies of electronic records, suitable for review, are made available; and (3) employees are held accountable and responsible for actions taken under their electronic signatures. If initial findings indicate the firm's electronic records and/or electronic signatures may not be trustworthy and reliable, or when electronic recordkeeping systems inhibit meaningful FDA inspection, a more detailed evaluation may be warranted. Districts should consult with center compliance officers and the Office of Enforcement (HFC-240) in assessing the need for, and potential depth of, more detailed part 11 coverage. When substantial and significant part 11 deviations exist, FDA will not accept use of electronic records and electronic signatures to meet the requirements of the applicable predicate rule. See Compliance Policy Guide (CGP), Sec.

160.850.

See IOM sections 594.1 and 527.3 for procedures for collecting and identifying electronic data.

Personnel - Part III, C.1.c. (21 CFR 58.29)

Determine the following:

- Who was involved in the design, development, and validation of the computer system?
- Who is responsible for the operation of the computer system, including inputs, processing, and output of data?
- If computer system personnel have training commensurate with their responsibilities, including professional training and training in GLPs.
- Whether some computer system personnel are contractors who are present on-site full-time, or nearly full-time. The investigation should include these contractors as though they were employees of the firm. Specific inquiry may be needed to identify these contractors, as they may not appear on organization charts.

QAU Operations - Part III, C.2 (21 CFR 58.35(b-d))

- Verify SOPs exist and are being followed for QAU inspections of computer operations.
- Facilities - Part III, C.3 (21 CFR 58.41 - 51)
- Determine that computerized operations and archived computer data are housed under appropriate environmental conditions.
- Equipment - Part III, C.4 (21 CFR 58.61 - 63)
- For computer systems, check that the following procedures exist and are documented:
- Validation study, including validation plan and documentation of the plan's completion.
- Maintenance of equipment, including storage capacity and back-up procedures.
- Control measures over changes made to the computer system, which include the evaluation of the change, necessary test design, test data, and final acceptance of the change.
- Evaluation of test data to assure that data is accurately transmitted and handled properly when analytical equipment is directly interfaced to the computer. and
- Procedures for emergency back-up of the computer system, (e.g., back-up battery system and data forms for recording data in case of a computer failure or power outage).
- Testing Facility Operations - Part III, C.5 (21 CFR 58.81)

- Verify that a historical file of outdated or modified computer programs is maintained.
- Records and Reports (21 CFR 58.185 - 195) (PART III C.10.b.)
- Verify that the final report contains the required elements in 58.185(a) (1-14), including a description of any computer program changes.
- Storage and Retrieval of Records and Data - Part III, C.10.c. (21 CFR 58.190)
- Assess archive facilities for degree of controlled access and adequacy of environmental controls with respect to computer media storage conditions.
- Determine how and where computer data and backup copies are stored, that records are indexed in a way to allow access to data stored on electronic media, and that environmental conditions minimize deterioration.
- Determine how and where original computer data and backup copies are stored.

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PART ONE:

OECD PRINCIPLES OF GOOD LABORATORY PRACTICE*

(as revised in 1997)

SECTION I

INTRODUCTION

Preface

Government and industry are concerned about the quality of non-clinical health and environmental safety studies upon which hazard assessments are based. As a consequence, OECD Member countries have established criteria for the performance of these studies.

To avoid different schemes of implementation that could impede international trade in chemicals, OECD Member countries have pursued international harmonisation of test methods and good laboratory practice. In 1979 and 1980, an international group of experts established under the Special Programme on the Control of Chemicals developed the "OECD Principles of Good Laboratory Practice" (GLP), utilising common managerial and scientific practices and experience from various national and international sources. These Principles of GLP were adopted by the OECD Council in 1981, as an Annex to the Council Decision on the Mutual Acceptance of Data in the Assessment of Chemicals [C(81)30(Final)].

In 1995 and 1996, a new group of experts was formed to revise and update the Principles. The current document is the result of the consensus reached by that group. It cancels and replaces the original Principles adopted in 1981.

The purpose of these Principles of Good Laboratory Practice is to promote the development of quality test data. Comparable quality of test data forms the basis for the mutual acceptance of data among countries. If individual countries can confidently rely on test data developed in other countries, duplicative testing can be avoided, thereby saving time and resources. The application of these Principles should help to avoid the creation of technical barriers to trade, and further improve the protection of human health and the environment.

* The OECD Principles of Good Laboratory Practice are contained in Annex II of the Decision of the Council concerning the Mutual Acceptance of Data in the Assessment of Chemicals [C(8 1)30(Final)] (See Part Two of this document for the text of that Council Decision). The 1981 Council Decision was amended in 1997, at which time Annex II was replaced by the revised Principles of GLP [C(97)186/Final].

1. Scope

These Principles of Good Laboratory Practice should be applied to the non-clinical safety testing of test items contained in pharmaceutical products, pesticide products, cosmetic products, veterinary drugs as well as food additives, feed additives, and industrial chemicals. These test items are frequently synthetic chemicals, but may be of natural or biological origin and, in some circumstances, may be living organisms. The purpose of testing these test items is to obtain data on their properties and/or their safety with respect to human health and/or the environment.

Non-clinical health and environmental safety studies covered by the Principles of Good Laboratory Practice include work conducted in the laboratory, in greenhouses, and in the field.

Unless specifically exempted by national legislation, these Principles of Good Laboratory Practice apply to all non-clinical health and environmental safety studies required by regulations for the purpose of registering or licensing pharmaceuticals, pesticides, food and feed additives, cosmetic products, veterinary drug products and similar products, and for the regulation of industrial chemicals.

2. Definitions of Terms

2.1 Good Laboratory Practice

1. Good Laboratory Practice (GLP) is a quality system concerned with the organisational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported.

2.2 Terms Concerning the Organization of a Test Facility

1. Test facility means the persons, premises and operational unit(s) that are necessary for conducting the non-clinical health and environmental safety study. For multi-site studies, those which are conducted at more than one site, the test facility comprises the site at which the Study Director is located and all individual test sites, which individually or collectively can be considered to be test facilities.
2. Test site means the location(s) at which a phase(s) of a study is conducted.
3. Test facility management means the person(s) who has the authority and formal responsibility for the organization and functioning of the test facility according to these Principles of Good Laboratory Practice.
4. Test site management (if appointed) means the person(s) responsible for ensuring that the phase(s) of the study, for which he is responsible, are conducted according to these Principles of Good Laboratory Practice.
5. Sponsor means an entity which commissions, supports and/or submits a non-clinical health and environmental safety study.
6. Study Director means the individual responsible for the overall conduct of the non-

clinical health and environmental safety study.

7. Principal Investigator means an individual who, for a multi-site study, acts on behalf of the Study Director and has defined responsibility for delegated phases of the study. The Study Director's responsibility for the overall conduct of the study cannot be delegated to the Principal Investigator(s); this includes approval of the study plan and its amendments, approval of the final report, and ensuring that all applicable Principles of Good Laboratory Practice are followed.
8. Quality Assurance Programme means a defined system, including personnel, which is independent of study conduct and is designed to assure test facility management of compliance with these Principles of Good Laboratory Practice.
9. Standard Operating Procedures (SOPs) means documented procedures which describe how to perform tests or activities normally not specified in detail in study plans or test guidelines.
10. Master schedule means a compilation of information to assist in the assessment of workload and for the tracking of studies at a test facility.

2.3 Terms Concerning the Non-Clinical Health and Environmental Safety Study

1. Non-clinical health and environmental safety study, henceforth referred to simply as "study", means an experiment or set of experiments in which a test item is examined under laboratory conditions or in the environment to obtain data on its properties and/ or its safety, intended for submission to appropriate regulatory authorities.
2. Short-term study means a study of short duration with widely used, routine techniques.
3. Study plan means a document which defines the objectives and experimental design for the conduct of the study, and includes any amendments.
4. Study plan amendment means an intended change to the study plan after the study initiation date.
5. Study plan deviation means an unintended departure from the study plan after the study initiation date.
6. Test system means any biological, chemical or physical system or a combination thereof used in a study.
7. Raw data means all original test facility records and documentation, or verified copies thereof, which are the result of the original observations and activities in a study. Raw data also may include, for example, photographs, microfilm or microfiche copies, computer readable media, dictated observations, recorded data from automated instruments, or any other data storage medium that has been recognized as capable of providing secure storage of information for a time period as stated in section 10, below.
8. Specimen means any material derived from a test system for examination, analysis, or retention.
9. Experimental starting date means the date on which the first study specific data are

collected.

10. Experimental completion date means the last date on which data are collected from the study.
11. Study initiation date means the date the Study Director signs the study plan. 12. Study completion date means the date the Study Director signs the final report.

2.4 Terms Concerning the Test Item

1. Test item means an article that is the subject of a study.
2. Reference item ("control item") means any article used to provide a basis for comparison with the test item.
3. Batch means a specific quantity or lot of a test item or reference item produced during a defined cycle of manufacture in such a way that it could be expected to be of a uniform character and should be designated as such.
4. Vehicle means any agent which serves as a carrier used to mix, disperse, or solubilize the test item or reference item to facilitate the administration/application to the test system.

SECTION II

GOOD LABORATORY PRACTICE PRINCIPLES

1. Test Facility Organization and Personnel

1.1 Test Facility Management's Responsibilities

1. Each test facility management should ensure that these Principles of Good Laboratory Practice are complied with, in its test facility.
2. At a minimum it should:
    a. ensure that a statement exists which identifies the individual(s) within a test facility who fulfill the responsibilities of management as defined by these Principles of Good Laboratory Practice;
    b. ensure that a sufficient number of qualified personnel, appropriate facilities, equipment, and materials are available for the timely and proper conduct of the study;
    c. ensure the maintenance of a record of the qualifications, training, experience and job description for each professional and technical individual;
    d. ensure that personnel clearly understand the functions they are to perform and, where necessary, provide training for these functions;
    e. ensure that appropriate and technically valid Standard Operating Procedures are established and followed, and approve all original and revised Standard Operating Procedures;
    f. ensure that there is a Quality Assurance Program with designated personnel and

assure that the quality assurance responsibility is being performed in accordance with these Principles of Good Laboratory Practice;

g. ensure that for each study an individual with the appropriate qualifications, training, and experience is designated by the management as the Study Director before the study is initiated. Replacement of a Study Director should be done according to established procedures, and should be documented.

h. ensure, in the event of a multi-site study, that, if needed, a Principal Investigator is designated, who is appropriately trained, qualified and experienced to supervise the delegated phase(s) of the study. Replacement of a Principal Investigator should be done according to established procedures, and should be documented.

i. ensure documented approval of the study plan by the Study Director;

j. ensure that the Study Director has made the approved study plan available to the Quality Assurance personnel;

k. ensure the maintenance of an historical file of all Standard Operating Procedures;

l. ensure that an individual is identified as responsible for the management of the archive(s);

m. ensure the maintenance of a master schedule;

n. ensure that test facility supplies meet requirements appropriate to their use in a study;

o. ensure for a multi-site study that clear lines of communication exist between the Study Director, Principal Investigator(s), the Quality Assurance Programme(s) and study personnel;

p. ensure that test and reference items are appropriately characterised;

q. establish procedures to ensure that computerised systems are suitable for their intended purpose, and are validated, operated and maintained in accordance with these Principles of Good Laboratory Practice.

3. When a phase(s) of a study is conducted at a test site, test site management (if appointed) will have the responsibilities as defined above with the following exceptions: 1.1.2 g), i), j) and o).

1.2 Study Director's Responsibilities

1. The Study Director is the single point of study control and has the responsibility for the overall conduct of the study and for its final report.
2. These responsibilities should include, but not be limited to, the following functions. The Study Director should:
    a. approve the study plan and any amendments to the study plan by dated

signature;

b. ensure that the Quality Assurance personnel have a copy of the study plan and any amendments in a timely manner and communicate effectively with the Quality Assurance personnel as required during the conduct of the study;
c. ensure that study plans and amendments and Standard Operating Procedures are available to study personnel;
d. ensure that the study plan and the final report for a multi-site study identify and define the role of any Principal Investigator(s) and any test facilities and test sites involved in the conduct of the study;
e. ensure that the procedures specified in the study plan are followed, and assess and document the impact of any deviations from the study plan on the quality and integrity of the study, and take appropriate corrective action if necessary; acknowledge deviations from Standard Operating Procedures during the conduct of the study;
f. ensure that all raw data generated are fully documented and recorded; ensure that computerized systems used in the study have been validated;
g. sign and date the final report to indicate acceptance of responsibility for the validity of the data and to indicate the extent to which the study complies with these Principles of Good Laboratory Practice;
h. ensure that after completion (including termination) of the study, the study plan, the final report, raw data and supporting material are archived.

1.3 Principal Investigator's Responsibilities

The Principal Investigator will ensure that the delegated phases of the study are conducted in accordance with the applicable Principles of Good Laboratory Practice.

1.4 Study Personnel's Responsibilities

1. All personnel involved in the conduct of the study must be knowledgeable in those parts of the Principles of Good Laboratory Practice which are applicable to their involvement in the study.
2. Study personnel will have access to the study plan and appropriate Standard Operating Procedures applicable to their involvement in the study. It is their responsibility to comply with the instructions given in these documents. Any deviation from these instructions should be documented and communicated directly to the Study Director, and/or if appropriate, the Principal Investigator(s).
3. All study personnel are responsible for recording raw data promptly and accurately and in compliance with these Principles of Good Laboratory Practice, and are responsible for the quality of their data.
4. Study personnel should exercise health precautions to minimize risk to themselves and

to ensure the integrity of the study. They should communicate to the appropriate person any relevant known health or medical condition in order that they can be excluded from operations that may affect the study.

2. Quality Assurance Program

2.1 General

1. The test facility should have a documented Quality Assurance Program to assure that studies performed are in compliance with these Principles of Good Laboratory Practice.
2. The Quality Assurance Program should be carried out by an individual or by individuals designated by and directly responsible to management and who are familiar with the test procedures.
3. This individual(s) should not be involved in the conduct of the study being assured.

2.2 Responsibilities of the Quality Assurance Personnel

1. The responsibilities of the Quality Assurance personnel include, but are not limited to, the following functions. They should:

a) maintain copies of all approved study plans and Standard Operating Procedures in use in the test facility and have access to an up-to-date copy of the master schedule;

b) verify that the study plan contains the information required for compliance with these Principles of Good Laboratory Practice. This verification should be documented;

c) conduct inspections to determine if all studies are conducted in accordance with these Principles of Good Laboratory Practice. Inspections should also determine that study plans and Standard Operating Procedures have been made available to study personnel and are being followed.

Inspections can be of three types as specified by Quality Assurance Program Standard Operating Procedures:

- Study-based inspections,
- Facility-based inspections,
- Process-based inspections.

Records of such inspections should be retained.

d) inspect the final reports to confirm that the methods, procedures, and observations are accurately and completely described, and that the reported results accurately and completely reflect the raw data of the studies;

e) promptly report any inspection results in writing to management and to the Study Director, and to the Principal Investigator(s) and the respective management, when applicable;

f) prepare and sign a statement, to be included with the final report, which specifies types of inspections and their dates, including the phase(s) of the study inspected, and the dates inspection results were reported to management and the Study Director and Principal Investigator(s), if applicable. This statement would also serve to confirm that the final report reflects the raw data.

3. Facilities

3.1 General

1. The test facility should be of suitable size, construction and location to meet the requirements of the study and to minimize disturbance that would interfere with the validity of the study.
2. The design of the test facility should provide an adequate degree of separation of the different activities to assure the proper conduct of each study.

3.2 Test System Facilities

1. The test facility should have a sufficient number of rooms or areas to assure the isolation of test systems and the isolation of individual projects, involving substances or organisms known to be or suspected of being biohazardous.
2. Suitable rooms or areas should be available for the diagnosis, treatment and control of diseases, in order to ensure that there is no unacceptable degree of deterioration of test systems.
3. There should be storage rooms or areas as needed for supplies and equipment. Storage rooms or areas should be separated from rooms or areas housing the test systems and should provide adequate protection against infestation, contamination, and/or deterioration.

3.3 Facilities for Handling Test and Reference Items

1. To prevent contamination or mix-ups, there should be separate rooms or areas for receipt and storage of the test and reference items, and mixing of the test items with a vehicle.
2. Storage rooms or areas for the test items should be separate from rooms or areas containing the test systems. They should be adequate to preserve identity, concentration, purity, and stability, and ensure safe storage for hazardous substances.

3.4 Archive Facilities

Archive facilities should be provided for the secure storage and retrieval of study plans, raw data, final reports, samples of test items and specimens. Archive design and archive conditions should protect contents from untimely deterioration.

3.5 Waste Disposal

Handling and disposal of wastes should be carried out in such a way as not to jeopardize the integrity of studies. This includes provision for appropriate collection, storage and disposal facilities, and decontamination and transportation procedures.

4. Apparatus, Material, and Reagents

1. Apparatus, including validated computerised systems, used for the generation, storage and retrieval of data, and for controlling environmental factors relevant to the study should be suitably located and of appropriate design and adequate capacity.
2. Apparatus used in a study should be periodically inspected, cleaned, maintained, and calibrated according to Standard Operating Procedures. Records of these activities should be maintained. Calibration should, where appropriate, be traceable to national or international standards of measurement.
3. Apparatus and materials used in a study should not interfere adversely with the test systems.
4. Chemicals, reagents, and solutions should be labelled to indicate identity (with concentration if appropriate), expiry date and specific storage instructions. Information concerning source, preparation date and stability should be available. The expiry date may be extended on the basis of documented evaluation or analysis.

5. Test Systems

5.1 Physical/Chemical

1. Apparatus used for the generation of physical/chemical data should be suitably located and of appropriate design and adequate capacity.
2. The integrity of the physical/chemical test systems should be ensured.

5.2 Biological

1. Proper conditions should be established and maintained for the storage, housing, handling and care of biological test systems, in order to ensure the quality of the data.
2. Newly received animal and plant test systems should be isolated until their health status has been evaluated. If any unusual mortality or morbidity occurs, this lot should not be used in studies and, when appropriate, should be humanely destroyed. At the experimental starting date of a study, test systems should be free of any disease or condition that might interfere with the purpose or conduct of the study. Test systems that become diseased or injured during the course of a study should be isolated and treated, if necessary to maintain the integrity of the study. Any diagnosis and treatment of any disease before or during a study should be recorded.
3. Records of source, date of arrival, and arrival condition of test systems should be maintained.
4. Biological test systems should be acclimated to the test environment for an adequate

period before the first administration/application of the test or reference item.

5. All information needed to properly identify the test systems should appear on their housing or containers. Individual test systems that are to be removed from their housing or containers during the conduct of the study should bear appropriate identification, wherever possible.
6. During use, housing or containers for test systems should be cleaned and sanitized at appropriate intervals. Any material that comes into contact with the test system should be free of contaminants at levels that would interfere with the study. Bedding for animals should be changed as required by sound husbandry practice. Use of pest control agents should be documented.
7. Test systems used in field studies should be located so as to avoid interference in
8. the study from spray drift and from past usage of pesticides.

6. Test and Reference Items

6.1 Receipt, Handling, Sampling and Storage

1. Records including test item and reference item characterization, date of receipt, expiry date, quantities received and used in studies should be maintained.
2. Handling, sampling, and storage procedures should be identified in order that the homogeneity and stability are assured to the degree possible and contamination or mix-up are precluded.
3. Storage container(s) should carry identification information, expiry date, and specific storage instructions.

6.2 Characterization

1. Each test and reference item should be appropriately identified (e.g., code, Chemical Abstracts Service Registry Number [CAS number], name, biological parameters).
2. For each study, the identity, including batch number, purity, composition, concentrations, or other characteristics to appropriately define each batch of the test or reference items should be known.
3. In cases where the test item is supplied by the sponsor, there should be a mechanism, developed in co-operation between the sponsor and the test facility, to verify the identity of the test item subject to the study.
4. The stability of test and reference items under storage and test conditions should be known for all studies.
5. If the test item is administered or applied in a vehicle, the homogeneity, concentration and stability of the test item in that vehicle should be determined. For test items used in field studies (e.g., tank mixes), these may be determined through separate laboratory experiments.
6. A sample for analytical purposes from each batch of test item should be retained for all

studies except short-term studies.

7. Standard Operating Procedures

7.1 A test facility should have written Standard Operating Procedures approved by test facility management that are intended to ensure the quality and integrity of the data generated by that test facility. Revisions to Standard Operating Procedures should be approved by test facility management.

7.2 Each separate test facility unit or area should have immediately available current Standard Operating Procedures relevant to the activities being performed therein. Published text books, analytical methods, articles and manuals may be used as supplements to these Standard Operating Procedures.

7.3 Deviations from Standard Operating Procedures related to the study should be documented and should be acknowledged by the Study Director and the Principal Investigator(s), as applicable.

7.4 Standard Operating Procedures should be available for, but not be limited to, the following categories of test facility activities. The details given under each heading are to be considered as illustrative examples.

1. Test and Reference Items

   Receipt, identification, labeling, handling, sampling and storage.

2. Apparatus, Materials and Reagents

   a) Apparatus

      Use, maintenance, cleaning, and calibration.

   b) Computerized Systems

      Validation, operation, maintenance, security, change control and back-up. c) Materials, Reagents and Solutions

      Preparation and labeling.

3. Record Keeping, Reporting, Storage, and Retrieval

   Coding of studies, data collection, preparation of reports, indexing systems, handling of data, including the use of computerized systems.

4. Test System (where appropriate)

   a) Room preparation and environmental room conditions for the test system

   b) Procedures for receipt, transfer, proper placement, characterisation, identification and care of the test system.

   c) Test system preparation, observations and examinations, before, during and at the conclusion of the study.

   d) Handling of test system individuals found moribund or dead during the

study.

e) Collection, identification and handling of specimens including necropsy and histopathology.

f) Siting and placement of test systems in test plots.

5. Quality Assurance Procedures

Operation of Quality Assurance personnel in planning, scheduling, performing, documenting and reporting inspections.

8. Performance of the Study

8.1 Study Plan

1. For each study, a written plan should exist prior to the initiation of the study. The study plan should be approved by dated signature of the Study Director and verified for GLP compliance by Quality Assurance personnel as specified in Section 2.2.1.b., above. The study plan should also be approved by the test facility management and the sponsor, if required by national regulation or legislation in the country where the study is being performed.
2. Amendments to the study plan should be justified and approved by dated signature of the Study Director and maintained with the study plan.
    a) Deviations from the study plan should be described, explained, acknowledged and dated in a timely fashion by the Study Director and/or Principal Investigator(s) and maintained with the study raw data.
3. For short-term studies, a general study plan accompanied by a study specific supplement may be used.

8.2 Content of the Study Plan

The study plan should contain, but not be limited to the following information:

1. Identification of the Study, the Test Item and Reference Item
    a) A descriptive title;
    b) A statement which reveals the nature and purpose of the study;
    c) Identification of the test item by code or name (IUPAC; CAS number, biological parameters, etc.);
    d) The reference item to be used.
2. Information Concerning the Sponsor and the Test Facility
    a) Name and address of the sponsor;
    b) Name and address of any test facilities and test sites involved;
    c) Name and address of the Study Director;
    d) Name and address of the Principal Investigator(s), and the phase(s) of the study

delegated by the Study Director and under the responsibility of the Principal Investigator(s).

3. Dates
   a) The date of approval of the study plan by signature of the Study Director. The date of approval of the study plan by signature of the test facility management and sponsor if required by national regulation or legislation in the country where the study is being performed.
   b) The proposed experimental starting and completion dates.
4. Test Methods

Reference to the OECD Test Guideline or other test guideline or method to be used.

5. Issues (where applicable)
   a) The justification for selection of the test system;
   b) Characterization of the test system, such as the species, strain, substrain, source of supply, number, body weight range, sex, age and other pertinent information;
   c) The method of administration and the reason for its choice;
   d) The dose levels and/or concentration(s), frequency, and duration of administration/ application;
   e) Detailed information on the experimental design, including a description of the chronological procedure of the study, all methods, materials and conditions, type and frequency of analysis, measurements, observations and examinations
   f) to be performed, and statistical methods to be used (if any).
6. Records

   A list of records to be retained.

8.3 Conduct of the Study

1. A unique identification should be given to each study. All items concerning this study should carry this identification. Specimens from the study should be identified to confirm their origin. Such identification should enable traceability, as appropriate for the specimen and study.
2. The study should be conducted in accordance with the study plan.
3. All data generated during the conduct of the study should be recorded directly, promptly, accurately, and legibly by the individual entering the data. These entries should be signed or initialed and dated.
4. Any change in the raw data should be made so as not to obscure the previous entry, should indicate the reason for change and should be dated and signed or initialed by the individual making the change.
5. Data generated as a direct computer input should be identified at the time of data input

by the individual(s) responsible for direct data entries. Computerized system design should always provide for the retention of full audit trails to show all changes to the data without obscuring the original data. It should be possible to associate all changes to data with the persons having made those changes, for example, by use of timed and dated (electronic) signatures. Reason for changes should be given.

9. Reporting of Study Results

9.1 General

1. A final report should be prepared for each study. In the case of short term studies, a standardized final report accompanied by a study specific extension may be prepared.
2. Reports of Principal Investigators or scientists involved in the study should be signed and dated by them.
3. The final report should be signed and dated by the Study Director to indicate acceptance of responsibility for the validity of the data. The extent of compliance with these Principles of Good Laboratory Practice should be indicated.
4. Corrections and additions to a final report should be in the form of amendments. Amendments should clearly specify the reason for the corrections or additions and should be signed and dated by the Study Director.
5. Reformatting of the final report to comply with the submission requirements of a national registration or regulatory authority does not constitute a correction, addition or amendment to the final report.

9.2 Content of the Final Report

The final report should include, but not be limited to, the following information:

1. Identification of the Study, the Test Item and Reference Item
    a) A descriptive title;
    b) Identification of the test item by code or name (IUPAC, CAS number, biological parameters, etc.);
    c) Identification of the reference item by name;
    d) Characterization of the test item including purity, stability and homogeneity.
2. Information Concerning the Sponsor and the Test Facility
    a) Name and address of the sponsor;
    b) Name and address of any test facilities and test sites involved;
    c) Name and address of the Study Director;
    d) Name and address of the Principal Investigator(s) and the phase(s) of the study delegated, if applicable;
    e) Name and address of scientists having contributed reports to the final report.

3. Dates

   Experimental starting and completion dates.

4. Statement

   A Quality Assurance Programme statement listing the types of inspections made and their dates, including the phase(s) inspected, and the dates any inspection results were reported to management and to the Study Director and Principal Investigator(s), if applicable. This statement would also serve to confirm that the final report reflects the raw data.

5. Description of Materials and Test Methods
   a) Description of methods and materials used;
   b) Reference to OECD Test Guideline or other test guideline or method.

6. Results
   a) A summary of results;
   b) All information and data required by the study plan;
   c) A presentation of the results, including calculations and determinations of statistical significance;
   d) An evaluation and discussion of the results and, where appropriate, conclusions.

7. Storage

   The location(s) where the study plan, samples of test and reference items, specimens, raw data and the final report are to be stored.

10. Storage and Retention of Records and Materials

10.1 The following should be retained in the archives for the period specified by the appropriate authorities:

   a. The study plan, raw data, samples of test and reference items, specimens, and the final report of each study;
   b. Records of all inspections performed by the Quality Assurance Programme, as well as master schedules;
   c. Records of qualifications, training, experience and job descriptions of personnel;
   d. Records and reports of the maintenance and calibration of apparatus;
   e. Validation documentation for computerised systems;
   f. The historical file of all Standard Operating Procedures;
   g. Environmental monitoring records.

   In the absence of a required retention period, the final disposition of any

study materials should be documented. When samples of test and reference items and specimens are disposed of before the expiry of the required retention period for any reason, this should be justified and documented. Samples of test and reference items and specimens should be retained only as long as the quality of the preparation permits evaluation.

10.2 Material retained in the archives should be indexed so as to facilitate orderly storage and retrieval.

10.3 Only personnel authorized by management should have access to the archives. Movement of material in and out of the archives should be properly recorded.

10.4 If a test facility or an archive contracting facility goes out of business and has no legal successor, the archive should be transferred to the archives of the sponsor(s) of the study(s).

Japan Ordinance 21 & PAB 424, 1997

Since PAB 424 serves to amplify and explain in more detail the provisions of Ordinance 21, the relevant sections of PAB 424 are inserted immediately after each Article in Ordinance 21, in italics. Note that differences in the English translations of specific terms, e.g. "manage" for "control", may be seen when PAB 424 references Ordinance 21. The interpretation of the ordinance is not affected, however.

GLP Ordinance No.2 1

a) The document is unofficial. Original Japanese document should be the official reference for the content.

b) Any outcome caused by the citation of this document is under the responsibility of Japan Society of Quality Assurance.

Ordinance Ministry of Health and Welfare Ordinance No.21, 1997

GLP standard ordinance for nonclinical laboratory studies on safety of drugs based on the provisions of Article 14 Paragraph 3 of the Pharmaceutical Affairs Law (Law No. 145, 1960) (with application mutatis mutandis of same article Paragraph 6, Article 19-2 paragraph 4 and Article 23 of the same Law) and Article 14-4 Paragraph 4 and Article 14-5 Paragraph 4 of the same Law (with application those provisions mutatis mutandis of Article 19-4 and Article 23 of the same Law) shall lay down as follows.

March 26, 1997 Ministry of Health and Welfare Junichiro Koizumi

GLP STANDARD ORDINANCE FOR NONCLINICAL LABORATORY STUDIES ON SAFETY OF DRUGS

Chapter 1: General Provisions

Article 1: **Aim**

This ordinance shall lay down good laboratory practices for nonclinical laboratory studies on safety of drugs (limited to the collection and preparation of Data concerning acute, sub-acute, chronic, teratology, and the other toxicity studies which are performed in testing facilities using test systems, in documents specified in Article 18-3 Paragraph 1 item 1 (d) (with application mutatis mutandis of Article 26-3 and Article 27) and Article 21-3 Paragraph 1 (with application mutatis mutandis of Article 26-13 and Article 27) of the Enforcement Regulations of the Pharmaceutical Affairs Law (Ministry of Health and Welfare Ordinance No. 1, 1961), and Article

14-5 Paragraph 3 of the Law (with application mutatis mutandis of Article 19-4 and Article 23 of the Law; the same hereinafter). The term is hereinafter abbreviated to "study" in standards specified by the Minister of Health and Welfare, based on Article 14 Paragraph 3 of the Pharmaceutical Affairs Law (Law No. 145, 1960 ; hereinafter referred to as "the Law" (with application mutatis mutandis of same Article Paragraph 6, Article 19-2 Paragraph 4 and Article 23 of the Law; the same hereinafter), and Article 14-4 Paragraph 4 and Article 14-5 paragraph 4 of the Law (with application those provisions mutatis mutandis of Article 19-4 and Article 23 of the Law; the same hereinafter).

Implementation of Ordinance on Standard of Conduct of Non-Clinical Studies of Drug Safety

Non-clinical studies which the persons, etc. perform to obtain approval of manufacture (import) of drugs have been guided by 'Good Laboratory Practice' (PAB Notification No.313, issued by the Director General, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, March 31, 1985). The Ordinance on standard for conduct of non-clinical studies on safety of drugs (MHW Ordinance No. 21, March 26, 1997, hereinafter referred to as the 'Ordinance') was laid down on the basis of Article 14 Paragraph 3, etc. of the Pharmaceutical Affairs Law (Law No. 145, 1961, hereinafter referred to as the 'Law') after revision by the law to partially revise the Pharmaceutical Affairs Law, etc. (Law No.104, 1996) and comes into effect from April 1, this year.

The purpose of the Ordinance is to specify compliance matters on non-clinical studies on safety of drugs which are performed by the person, etc. who wish to obtain approval of manufacture (import) so that such studies are conducted properly to assure the reliability of data of non-clinical studies on safety of drugs.

Compliance with the Ordinance is very important for proper and smooth conduct of non-clinical studies on safety of drugs. Therefore, please make the Ordinance thoroughly known to all industries concerned under your supervision with attention being paid to the following points.

1. *Scope and time of application of the Ordinance*

   1) *Scope of application*

   The Ordinance shall be applied to attached or submitted data of non-clinical studies on safety of drugs which manufacturers, importers, recipient of approval for foreign manufacturing, or in-country caretakers (hereinafter referred to as 'manufacturers etc.') perform for application for approval of manufacture (import) of drugs application for partial change, re-examination, and re-evaluation (herein after referred to as 'approval application, etc.'). The ordinance shall not be applicable to preliminary studies, such as dose-finding studies, etc. For range of drugs applied, see Article 18-4-2 of the Enforcement Regulations of the Pharmaceutical Affairs Law (MHW Ordinance No. 1, 1961).

   2) *Time of application*

   Good Laboratory Practice The Ordinance shall be applied to approval application, etc. submitted on and

after April 1, 1997. The Ordinance follows the contents of the previous notification and shall be applied to studies completed on and before March 3 1, 1997 and the studies already started.

2. Handling of existing notification

'Good Laboratory Practice' (PAB Notification No. 3 13, issued by the Director General, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, March 3 1, 1982) has been applied to non-clinical studies on safety of drugs since April 1, 1983, but shall be abolished on Apri1, 1997.

Article 2: **Definition**

1. In this ordinance, test article is any of drug, chemical or biological substance, or any product thereof which is subject for safety assessment.
2. In this ordinance, control article is any of drug, chemical or biological substance, or any product thereof to be tested for the purpose of comparison with test article.
3. In this ordinance, test system is any of animal plant, microorganism or composition to which test or control article is administered or added, or used as control to the test system for test article.
4. In this ordinance, specimen is any of materials collected from a test system for examination or analysis.
5. In this ordinance, raw data are the observation results and records obtained in a study.

'Raw data' in Paragraph 5 shall mean worksheet, notes, memorandums, or their exact transcripts which are required for the reconstruction and evaluation of the final reports, and include photos, microfilms, microfiche, computer records, magnetic records of dictated observation results, study results recorded by automated instruments, etc.

Article 3: **Conduct of study**

As for collection and preparation of materials stipulated in Paragraph 3 of Article 14, Paragraph 4 of Article 14-4, and Paragraph 4 of Article 14-5 in relation with study conducted by those who are attempted to get or have got approval under Article 14 (including the cases when Article 23 is applied), Articles 4 to 18 shall be followed.

Article 4: **Responsibilities of sponsor**

1. A person who commissions a study shall notify in advance a person who will accept the study that the study must be conducted in compliance with the provisions of this ordinance.
2. In relation with the preceding paragraph, a person who commissioned a study or a person who takes over the position (hereinafter called the "sponsor") should assure

that the study is or was conducted in ompliance with this ordinance.

3. The notification in the first paragraph and the confirmation in the preceding paragraph should be prepared and preserved in writing.

'Confirmation' in Paragraph 2 can be made by appropriate methods according to each case, and the client does not necessarily visit the trustee for on-site review. Notification of 'records by documents' in Paragraph 3 can be recorded by entering a contract or other document.

Chapter 2: Personnel and Organization

Article 5: **Personnel**

1. All of those to be engaged in the conduct of a study or belongs to quality assurance unit which will be specified in the following Article 6, Item 2 shall have received education or training, otherwise possess job experience necessary to perform the job, and be capable of performing the assigned function.
2. All of those to be engaged in a study shall take sanitary and health precautions necessary to avoid contamination of test, control articles and test systems.

'Hygienic precautions' shall include use of wears suitable for implementation of work of employees engaged in studies, report a person having a disease with the potential of adverse influence on the reliability of studies to the superior, and prohibition of such person from being engaged in studies until improvement of health status.

Article 6: **Management**

Management who is responsible for the management and administration of the testing facilities shall:

1. for each study, assign those in charge of the implementation, recording, and reporting etc. among those who are engaged in the study (hereinafter called the "study director");
2. designate a responsible person (hereinafter called the "quality assurance manager") for the unit hereinafter called the "quality assurance unit") which assures that studies at the testing facilities were conducted in compliance with this ordinance;
3. assure that the quality assurance manager fulfills his/her duties appropriately;
4. assure that test and control articles or mixture thereof have been appropriately tested for identity, strength, purity, stability and uniformity;
5. assure that facilities and equipment are used as following the standard operating procedures and protocol;

6. assure that a sufficient number of personnel is available to conduct the study appropriately;
7. conduct a necessary education and training to the personnel engaged in the conduct of a study and belongs to the quality assurance unit;
8. prepare and maintain documents on education and training, and job description for personnel engaged in the conduct of a study and belongs to the quality assurance unit;
9. in addition to those specified above, other duties to manage and administrate the testing facilities.

'Designation' in Paragraph 1 Item 2 shall include designation at change of the study director.

Article 7: **Study Director**

Study director shall:

1. assure that each study is conducted as following this ordinance, the standard operating procedures, and protocol;
2. assure that all raw data is recorded accurately, and appropriate actions are taken;
3. confirm that unexpected events that may adversely affect the reliability of study, also the actually implemented corrective actions are documented;
4. conduct improvements by implementing the actions specified in the following article 8-1-3 and recommendations in item 3 of the same;
5. assure that test systems are the same as specified in the protocol;
6. assure that the protocol, records of specimens, raw data and others, final report, and documents describing changes or amendments to the final report are stored in the archives for materials related to study (hereinafter called "study related materials").
7. manage other duties in relation with study such as implementation, recording and reporting.

Article 8: **Quality Assurance Unit**

1. The quality assurance manager should implement by oneself, or designate a person in charge of study to implement the following:
    1) maintain a copy of documents which were prepared by test article to identify the sponsor (or a corporate body), study director, test system, the nature of study, current status of study, status of final report of all studies conducted at the testing facilities;

2) maintain a copy of the protocols and standard operating procedures;
3) confirm that inspections are conducted periodically at intervals appropriate to assure the reliability of study in compliance with this ordinance; prepare records specifying the nature of inspection, inspection results, actions taken to solve problems, and the date when re-inspection is scheduled etc., then store them with signature or sign and seal;
4) report any significant problems which may affect the reliability of study found during the course of an inspection conducted under the preceding item hereof to the management and study director, and recommend actions to solve the problems;
5) prepare a report on problems and corrective actions taken to solve the problems, and submit it to the management and study director;
6) assure that the confirmation by the study director is conducted appropriately according to Article 7, Paragraph 3.
7) review final report to assure that it accurately describes the testing method and reflects
raw data of the study, then report the review results to the management and study director;
8) prepare and signature or sign and seal a document which indicates the dates when the confirmation (described in item 3 and preceding item) took place, and that the review results were reported to the management and study director;
9) record in writing the way to organize documents at the quality assurance unit, and preserve the record;
10) other duties which are necessary to assure that tests conducted at the testing facilities comply with this ordinance.

2. A person in charge of a study at the quality assurance unit shall be the one who is not involved in the conduct of the study.

3. The documents identified in paragraph 1 hereof must be preserved at the testing facilities, otherwise at a site designated by the sponsor.

Chapter 3: Testing facilities and equipment

Article 9: **Testing facilities**

1. Testing facilities shall be designed of suitable size and structure, also be located sufficiently away from the things which may affect the conduct of study, to function appropriately.

2. Testing facilities where animal study is conducted shall include breeding facility and storage for diets and other supplies, to breed and manage animals appropriately.

3. Testing facilities shall have divided areas each for handling test and control articles, for

study operations, and for conducting other studies appropriately.

4. Testing facilities shall have archives.

'Animal care facilities' shall be ones which fulfill the following items, where applicable.

a) Separated housing by species or study system

b) Separated housing by protocol

c) Quarantine of animals

d) Routine of specialized housing of animal

'Animal supply facilities' in Paragraph 2 shall have the function of storage area for feed, bedding, supplies, and equipment, where necessary

'Other necessary facilities-in Paragraph 2 shall include the following items:

a) Animal rooms or areas where studies using volatile substances, radioactive substances, infectious agents, etc. can be performed in isolation from other animal care facilities.

b) Facilities for isolation and treatment of diseased animals

c) Facilities for collection and sanitary disposal, or for safe and sanitary storage of waste before discharge from the testing facilities.

'Facilities for handling test articles, etc.' shall be designed to fulfill the following items and to maintain the quality of the test and control articles as necessary to prevent contamination of mix-up of these articles.

a) Receipt and storage of the test and control articles

b) Mixing of the test or control article with a carrier

c) Storage of the test or control article mixture with a carrier

'Laboratory operation areas' shall mean separate spaces for the performance of periodical measurements and other operations such as biochemical test, histopathology, etc.

'Separated areas for proper performance of other studies' shall include the following.

a) Isolated areas where subparts of animals or microorganisms which may be subject to biohazard control

b) Separated areas for cleaning, sterilizing, and storing supplies and equipment used during the course of studies.

Article 10: **Equipment**

1. Equipment for collection, measurement and analysis of study records, equipment for preserving the environment surrounding the testing facilities, and other equipment necessary to conduct study (hereinafter called the "equipment") shall be designed appropriately with sufficient processing capabilities.
2. The equipment shall be installed appropriately for convenient operation, inspection, maintenance, cleaning and repair.
3. When the inspection, maintenance, and repair in the preceding paragraph are conducted, the dates, content and operators shall be recorded in writing and preserved.

Equipment used for collecting, measuring, or analyzing test data shall undergo tests, calibration, and standardization properly, where applicable.

Chapter 4: Operation at testing facilities

Article 11: **Standard Operating Procedures**

1. The management shall prepare the SOP for the method and work flow of the items as follows:

Administration of test and control articles

1) Maintenance and repair of testing facilities and equipment
2) Control of animal care facilities
3) Breeding and control of experimental animals
4) Observation of general symptoms etc. in experimental animals
5) Operation, measurement, examination and analysis of study
6) Handling of moribund or dead animals
7) Necropsy and postmortem examination of animals
8) Collection and identification of specimens
9) Histopathological examination
10) Administration of raw data
11) Activities by the quality assurance unit
12) Health management of those engaged in study
13) Other necessary items

2. Management shall locate the standard operating procedure for each of above mentioned items at the site where it is operated.
3. When the standard operating procedure is to be changed, the management shall describe the date and preserve the original standard operating procedure prior to the change in the testing facilities.
4. Those engaged in study shall obtain approval by the study director for unavoidable deviation

from the standard operating procedure.

5. Those engaged in study shall describe on raw data that the standard operating procedure was not followed as stated in the preceding paragraph.

The management shall assume responsibility for compilation of standard operating procedures.

References, etc. can be used as supplementary to standard operating procedures.

'Management' in Paragraph Item 1 shall include receipt, labeling, storage, handling, mixing with a carrier, sampling, etc.

'Maintenance, inspection, and repair of equipment' shall clearly indicate methods and schedule of inspection, cleaning, maintenance, test, calibration, and standardization, and procedures of repair taken in case of failure or insufficiency of equipment.

Article 12: **Animal care**

1. Those engaged in study shall house all animals newly received from outside in isolated animal facilities where infection of any disease to other animals can be prevented, then observe and record abnormality of the animals.
2. Those engaged in study shall not use animals which are seen during the observation or study in the preceding paragraph to have disease or condition that may affect the conduct of the study.
3. Those engaged in study shall take necessary measures to have experimental animals conform to the testing environment.
4. Those engaged in study shall take necessary measures to identify individual animals so as to prevent erroneous housing of animals to be used in the study.
5. Those engaged in study shall conduct sanitary control of breeding facilities and animal supplies etc.

'Isolated' animals pursuant to the provisions of Item 2 may be authorized by the study director and treated provided that such treatment does not interfere with studies, where necessary. In this case, reason of treatment, authorization of such treatment, description treatment, drugs used for treatment, date of treatment, and the results of treatment, etc. shall be recorded and retained.

'Necessary measures' in Paragraph 4 shall include the following items.

a) Information for identification of each animal within an animal room shall be indicated clearly on the outside of cages, pens or racks.

b) Animals of different species shall be housed in separate rooms, as a rule.

c) *If animals of the same species used in different studies are housed in the same room, adequate differentiation by species and identification shall be made.*

'Sanitary manage' in Paragraph 5 shall include the following items.

a) *Necessary measures shall be taken at appropriate intervals so that animal cages, pens, racks, and accessory equipment are kept clean and sanitary.*

b) *Bedding used in animal cages or pens shall not interfere with the purpose or conduct of studies and shall be changed as often as necessary to keep the animal dry and clean.*

c) *Feed and water used for animals shall be analyzed periodically to ensure that contaminants known to be capable of interfering with studies and reasonably expected to be present in such feed or water are not present at levels above those specified in the protocol. Records of such analysis shall be retained as raw data.*

d) *Cleaning or pest control materials that may interfere with proper conduct of studies shall not be used. e) If any cleaning or pest control materials are used, the use shall be recorded.*

Chapter 5: Handling of test article

Article 13: **Handling of test and control articles**

1. Those engaged in study shall conduct appropriate control of test and control articles through measurement of characteristics and stability, and with accurate labeling etc.
2. Those engaged in study shall make appropriate use of the mixture of test or control article with media through measurement of characteristics and uniformity of test or control article.
3. Those engaged in study shall record the dates and amount of test or control article to be distributed, received, returned and discarded.

'Proper management' in Paragraph 1 shall include the following items.

a) *There is proper storage areas.*

b) *Distribution is made in a manner to preclude the possibility of contamination or deterioration of quality.*

c) *Proper labeling is made throughout the distribution process.*

d) *A testing facility shall determine and record the identity, content or strength, purity, composition, or other characteristics which specify the test and control articles for each lot before the initiation of studies, as a rule. In those cases where marketed products are*

used as the control article, characteristics specifying the substance may be substituted by their labeling.

e) The stability of the test of control article shall be determined before the initiation of studies, as a rule. If there are some circumstances which make it difficult to determine the stability before the initiation of studies, standard operating procedures for the stability testing shall be compiled and followed to provide for periodic analysis of each lot.

f) The name, abbreviated name, code number, and lot number shall be indicated clearly on each storage container of the test or control article as well as expiration date, if any, and storage conditions when special conditions are required. In those cases where storage containers are exclusively used for the test article, the fact shall be designated.

'Properly use by measurements, etc.' shall include the following items.

a) When the test of control article is mixed with a carrier before use, the stability of the test of control article in a mixture shall be determined before the initiation of administration. If there are some circumstances which make it difficult to determine the stability before the initiation of administration, standard operating procedures for the stability testing shall be compiled and followed to provide for periodic analysis the uniformity of the test article, etc. shall be determined before the initiation of studies, and the concentration of the test or control article in a mixture shall be determined periodically, where necessary.

b) Where any of the components in a mixture has an expiration date, the date shall be indicated on the container. If more than one component have expiration dates, the earliest date shall be indicated.

Article 14: Reagents and solutions

Those engaged in study shall make appropriate labels for storing conditions and expire dates of sample drug and solution, and use them appropriately according to their characteristics and use method etc.

Chapter 6: Protocol and conduct of study

Article 15: **Protocol**

1. Study director shall prepare protocol per study stating the following, and have the management (the sponsor and management when the study is entrusted to an external agent; the same will be applied to all of the following items):
    1) Title and purpose of study

2) Name and address of testing facilities
3) Name and address of the sponsor when the study is entrusted to an outside agent (name and location of the main office if it is entrusted to a corporate body)
4) Name of the study director
5) Information on test and control articles
6) Information on test system
7) Information on study procedure
8) Statistical method employed in analysis of raw data
9) Other records and materials to be preserved
10) Signature or sign and seal of the management and study director, and the dates
11) Other points necessary to plan study

2. When the protocol is to be changed, the study director shall record in writing when, where and why the change was made, then preserve the record with the protocol with signature or sign and seal.

The study director shall assume responsibility of compiling the protocol.

Each item of Paragraph 1 shall include the following contents.

a) For 'matters relating to the test and control articles' in Item 5, the name, abbreviated name, or code number.

b) For 'matters relating to test systems' in Item 6, species, strain, number, age, sex, body weight range, and source of supply, reason for selection, and identification method

c) For 'matters relating to conduct of studies' in Item 7, experimental design for the control of bias, environmental conditions for the study system, name and code number of feed (The description shall include specifications for acceptable levels of contaminants that are assumed to be present and interfere with the purpose or conduct of studies, if present above certain levels.), solvents, emulsifiers, and other materials used as carriers for dissolution of suspension of the test or control article, administration of the test and control article and the reason for selection of administration, the dose of the test and control articles, administration methods, frequency and duration of administration, and the reason for their selection, the name of guideline for toxicity studies to be followed (if applicable), the type, frequency, method, and schedule of observation, measurement, tests, and analyses to be performed.

Article 16: **Conduct of study**

1. Study shall be conducted appropriately according to the protocol and SOP under direction and

guidance by the study director.

2, All those engaged in study shall appropriately record all raw data with the author's name and date.

3. When raw data is to be corrected, those engaged in study shall state why, who and when the correction was made, and make the correction appropriately.

4. When unexpected things happen during study, those engaged in the study shall promptly report them to the study director, take measures for the improvement, and document the measures.

'Properly perform' in Paragraph 1 shall include the following items.

a) Each study shall have unique identification, and records of studies, specimens, etc. shall be accompanied by such identification.

b) Specimens shall be accompanied by the type of study, identification number of study system, and date of collection by a proper method.

c) Records of gross necropsy findings for a specimen shall be available to a person in charge when examining that specimen histopathologically.

'Properly record' in Paragraph 2 shall include the following items:

Raw data shall be recorded directly and immediately with legible, and hardly erasable means, except those generated as direct computer input.

In the case of direct computer input, date of inputting raw data and the person performing input shall be recorded. 'Properly correct' in Paragraph 3 shall include the following items:

Any change in raw data entries shall be made so as not to obscure the original entry, and shall indicate the reason for such change, and the date of the change, and the person making the change shall be identified by signature or seal at the time of change. Any change in computer entry shall be made so as not obscure the original entry, and shall indicate the reason for the change, and the date and the name of the person making the change.

Chapter 7: Report and storing

Article 17: **Final Report**

1. The study director shall prepare a final report for each study to include the following:

   1) Title and purpose of study

2) Name and address of testing facilities

3) First and final dates of study

4) Name of study director and others engaged in study

5) Information on test and control articles

6) Information on test systems

7) Unexpected study circumstances that may affect the reliability of the study and deviation from the protocol

8) Study methods

9) Statistical method employed in analysis of raw data

10) Study results, discussions and summary

11) The location to store raw data and specimens

12) Signature or sign and seal, and date by study director

13) The documents prepared by study director with signature or sign and seal according to Article 8-1-8

14) Other necessary items

2. When a final report is to be revised, the study director shall record in writing when, where and why the correction was made, and store it with the revised final report with signature or sign and seal.

The study director shall assume responsibility for compiling the final report.

Each item of Paragraph 1 shall include the following contents.

a) For 'names of the study director and other persons engaged in the study' in Paragraph 4, tasks allotted.

b) For 'matters relating to the test article and control articles' in Paragraph 5, their names, abbreviated name or code numbers, and lot numbers, identification, content or strength, purity, composition, etc. which specify such articles, and stability under the administration conditions. c) For 'matters relating to study system' in Paragraph 6,

species, strain, number, age, sex, body weight range, source of supply, date of receipt, and animal care conditions.

c) *For 'matters relating to conduct of study' in Paragraph 8, administration route, dose, administration methods, frequency of administration, and duration of administration and dose of the test or control article, and the reason for decision, type, frequency, and methods of observation, measurement, tests, and analyses performed.*

Article 18: **Storing of study related materials**

1. The management shall store study related materials in archives appropriately.
2. The management shall have under him/her a person responsible for archives (hereinafter called the "archive manager").
3. Nobody but those designated by the archive manager shall enter archives.
4. The management shall transfer the study related materials to his successor or the sponsor etc. (hereinafter called the "successor") .when the use of the testing facilities is abolished or disrupted.
5. The provisions of paragraph 1-3 will be applied to the successor.

'Properly store' in Paragraph 1 shall include the following contents.

When specimens of raw data are retained separately from the final report that shall be recorded at the archives for the final report.

Study related data shall retained orderly for expedient retrieval with, indexes by the test article, study system, and type of study, etc.

Study related data specified in Paragraph 1 shall be retained for the periods specified in Article 26-2- 3 (including application mutatis mutandis in Article 27), Article 26-5 Item 3, and Article 26-12 of the Enforcement Regulations of the Pharmaceutical Affairs Law. However, wet specimens and specifically prepared specimens whose quality changes markedly during storage, such as histopathological specimens, electron microscopic specimens, and blood specimens shall be retained only as long as their quality afford evaluation.

Additional provision

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