Korean J. of Toxicology
Vol.1, No.1, p31-41, 1985

GOOD LABORATORY PRACTICE -PRINCIPLES AND PRESENT STATUS IN JAPAN-

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=ABSTRACT=

The Japanese Good Laboratory Practice (GLP) Standard on Drugs was finalized as a guideline and implemented in April, 1983.

This standard is intended to ensure the quality and integrity of the data from nonclinical toxicity studies submitted to the Ministry of Health and Welfare in support of applications for approval to manufacture or import new drugs or to be used in the reevaluation of previously approved drugs. The standard includes a guideline for organizational matters, personnel, facility, equipment, testing operation, documentation and conduct of studies.

Principles and influences of implementation of Japanese GLP will be discussed briefly in comparison with foreign GLPs.

Key Word: *Good laboratory practice standard, GLP, Drug toxicity*

INTRODUCTION

The flood of developments in research and the production of new drugs and other chemicals since the mid-1950s has not yet reached its crest but it has greatly increased the number and volume of chemicals found in clinical use and in the environment. Pharmaceuticals are essential chemicals which are developed for the direct application to humans and are under rigid control of the governments of many countries to ensure their safety.

During 1975 the House Health Subcommittee in the United States found some deficiencies in the final reports on drug tests submitted by a manufacturer to the Food and Drug Administration (FDA) for approval, such as improper handling of experimental animals and analysis of data. On the other hand, the General Accounting Office also found similar problems during an examination of data from a carcinogenicity test on a color additive performed in a governmental institute. On the basis of their investigatory inspection of several pharmaceutical industries and private contract laboratories, the FDA proposed the legislation of Good Laboratory Practice (GLP) in November of 1976 to ensure the integrity of data from toxicity experiments in the preclinical stage. Deficiencies indicated by the FDA after preliminary inspections of these laboratories were improper laboratory procedures and animal care, loss of original data and tissue slides, mistakes in transcription of raw data, non-adherence to protocols, faulty analysis of data, etc. The final draft of the

GLP regulations for nonclinical laboratory studies were issued on December 22,1978 in accordance with the Federal Food, Drug and Cosmetic Act and other applicable laws. After public hearings were held and proposals for revision examined, the amended GLP regulations were implemented as of June 20, 1979.

The U.S. GLP regulations apply to the conduct of nonclinical laboratory studies that support or are intended to support applications for research or marketing permits for products regulated by FDA. These include food and color additives, human and animal drugs, medical devices for human use, biological products and electronic products.

In Japan, the Ministry of Health and Welfare (MHW) responded promptly to the FDA proposal of GLP regulation and the Director-General of the Pharmaceutical Affairs Bureau issued a Notice to ensure the reliability of data in October, 1976. This Notice applied to the handling of data from preclinical animal experiments on drugs which were submitted to the MHW with requests for approval to manufacture (import) of new drugs. In 1978, the MHW established an investigation committee on GLP that included 11 experts. The committee examined the issues for three years before proposing the Japanese GLP standard on June 20, 1981. The proposal was issued as a guideline on March 30, 1982, and implemented as of April 1 of 1983. Contrary to the GLP regulations of the FDA, the Japanese GLP standard is applied only to drugs regulated by the Pharmaceutical Law.

SCOPE

The Japanese GLP Standard for Safety Studies on Drugs should be applied to testing of pharmaceuticals to obtain data on their safety with respect to human health, and those data should be developed for the purpose of meeting regulatory requirements.

To ensure the quality and integrity of the safety data submitted to MHW in support of the approval of manufacture (import) and reevaluation of new drugs, Japanese GLP Standard prescribes guidelines for the conduct of studies in experimental animals and microorganisms or subparts thereof.

The Standard should be applied to the following studies:

Acute toxicity
Subacute toxicity
Chronic toxicity
Reproduction
Dependence liability
Antigenicity
Mutagenicity
Carcinogenicity
Local irritation

For the evaluation of toxicity of drugs or chemicals, valid data collection and study documentation are essential, and so the principles for proper conduct of study procedures, practices and laboratory conditions are required. GLP's are directed primarily towards the process of toxicity testing rather than towards the determination of the objective of the study or towards formation of a conclusion from a set of data.

GLP is concerned with the organizational process and the conditions under which experimental studies in the laboratory are performed, the Standard is not applicable to studies which do not involve proof of safety, nor is it applicable to human trials.

The Japanese GLP Standard consists of eight chapters including twenty nine articles for the conduct of these nonclinical studies in relation to hard (facilities and equipments) and soft (personnel, organization, quality assurance, standard operating procedures, records and reports) matters.

I. General Provision

Chapter I of the Japanese GLP Standard prescribes the purpose, definitions of terms, applicability to studies performed under contracts, and inspection of testing facilities.

Article 1 (Purpose) It is stressed that this Standard prescribes good laboratory practices for nonclinical laboratory studies that are conducted to support the application for approval to manufacture (or import) drugs under the provisions of the Enforcement Regulations of Pharmaceutical Affairs Law so that in all studies the reliability of safety data shall be assured.

Article 2 (Definition) For definition of the terms used in the Standard, twelve terms such as nonclinical laboratory study, test and control articles (substances), test-system (animal), specimen, raw data, testing facility, sponsor, management, study director and quality assurance unit, etc., are included.

Article 3 (Notification to a contract laboratory by a sponsor.) When a sponsor arranges for the performance of a study by a contract laboratory, it shall notify the laboratory that the study must be conducted in compliance with this Standard.

Article 4 (Inspection) When the Minister of Health and Welfare or a prefectural governor orders the inspection of a testing facility by designated officials to assure the reliability of data, the facility shall permit inspection of all records, specimens, etc., which are required to be retained for the scheduled period under this Standard.

II. Personnel and Organization

Article 5 (Personnel) In reference to personnel, the Standard requires that all personnel should have education, training, and job experience sufficient for the performance of the assigned functions. The testing facility shall prepare and maintain records of education, training, and job experience, and a job description for each individual engaged in or supervising a study. A sufficient number of personnel should be available in the facility for the proper conduct of a study according to the protocol. Personnel shall take appropriate measures for good personal hygiene to ensure their own health and to avoid the contamination of the test system. Any medical condition which may adversely affect the integrity or quality of the study should be reported to supervisory personnel.

Article 6 (Management) The testing facility management must designate a study director and quality assurance unit before a study is initiated; ensure the quality of articles; and ensure the availability of personnel, resources, facilities, equipment, and materials. Management also has to assure that any deviation from this Standard reported by the quality assurance unit is also reported to the study director and that corrective actions are taken and recorded.

Article 7 (Study director) An individual designated for each study by management should be responsible for the overall conduct of the study, should take the lead in study control and should be responsible for the technical conduct of the study; the interpretation, analysis and recording of data; and the reporting of the study results. The study director has to assure the compliance of the study to this Standard; that the protocol is approved by management; that all experimental data are accurately recorded; and that records, reports or specimens are transferred to the archives during or at the close of the study.

Article 8 (Quality assurance unit, QAU) This shall be composed of one or more people designated by the management or sponsor to perform the duties relating to quality assurance of studies. The QAU does not evaluate the study nor the final report technically, but it assures that the final report accurately describes the study results. The QAU should maintain a copy of a master schedule sheet of all studies conducted at the testing facility, copies of protocols, and copies of standard operating procedures. The QAU has to inspect each phase of a study periodically, (the frequency of inspection varies with the term of each study but it should be often enough to ensure study quality). It should prepare status reports for each study, noting problems and corrective actions taken, and submit these to the management and study director.

III. Facilities

Article 9 The key points for these sections relate to the provision of facilities of adequate size and number to prevent any function or activity from having an adverse impact on the proper conduct of a study.

Article 10 (Animal care facilities, etc)Animal I care facilities shall include a sufficient number of animal rooms or areas to allow separation of species or test systems and isolation of individual projects; a quarantine area; areas for isolation and treatment of diseased animals; and appropriate provision for the collection and sanitary disposal of all wastes.

Article 11 (Animal supply facilities) A testing facility shall have storage areas for feed and bedding which are separated from areas for housing test systems, and which are protected from contamination. Storage areas for supplies and equipment shall also be provided.

Article 12 (Facilities for handling test and control articles) For handling test and control articles (any drug, chemical or biological substance or any products thereof to be studied) a testing facility shall have specified areas for the receipt,

storage and mixing of these articles with a carrier, and shall preserve the quality of these materials.

Article 13 (Laboratory operation areas) A testing facility shall have separate laboratory space for biochemical tests, histopathology, surgery and necropsy, and for utilizing subparts of animals or microorganisms. Separate space for cleaning, sterilizing and maintaining supplies and equipment shall also be provided.

Article 14 (Archives) For storage and retrieval of protocols, specimens, raw data, documentation records and final reports, a testing facility is required to have archives.

Article 15 (Administrative facilities, etc.) Space shall be provided for administration, supervision and direction of the testing facility.

IV. Equipment

Article 16 The basic principles in this chapter are that equipment used in a study shall be of appropriate design and adequate capacity to function according to the protocol and the standard operating procedure (SOP).

Article 17 All equipment in a test facility should be suitably located, maintained, cleaned and calibrated to ensure optimal function in use.

Article 18 To assure the accuracy and precision of measurement, equipment shall be standardized periodically and/or before use, and maintained in good repair. Written SOP's should describe in detail methods for the appropriate operation, inspection, adjustment and maintenance of equipment. They should also prescribe remedial actions to be taken if such are necessary. The SOP also shall indicate the person responsible for care of that piece of equipment. Written records of the inspection, maintenance, and repair of equipment shall be prepared and maintained.

V. Testing Facilities Operation

Article 19 (Standard operating procedures, SOP) Written standard operating procedures (SOP's) are essential to ensure the reliability of the data; the adequacy and appropriateness of an SOP is the major responsibility of management. Published literature may be used as a supplement to an SOP.

SOP's shall be established for the following items:

(1) Receipt, labelling and storage of test and control articles and method of mixing with a carrier.
(2) Animal room preparation and animal care.
(3) Maintenance and repair of facilities and equipment.
(4) Identification., housing, placement and transfer of animals.
(5) Test system observations.
(6) Methods of measurement, laboratory tests and analysis.
(7) Handling of moribund or dead animals.
(8) Necropsy or postmortem examination of animals.
(9) Collection and identification of specimens.

(10) Histopathology.
(11) Data handling, storage and retrieval.

SOP's shall be available at each laborotory area where study operations are made. Deviations from SOP shall be approved by the study director and documented in the raw data; significant changes in SOP's shall be approved in writing by the management. The original and all revisions of SOP shall include the effective data; copies of each shall be retained in the archives.

Article 20 (Reagents and Solutions) prescribes guidelines pertaining to all reagents and solutions in the laboratory. It specifies that each be labelled to indicate identity, concentration, storage requirements and expiration date.

In **Article 21** general procedures pertaining to animal care such as acclimatization to the study environment, identification, separation by species or sex difference, protection of animals from contamination, isolation of diseased animals from healthy animals, etc., are prescribed.

VI. Test and Control Articles

A test article is defined in this Standard as any drug, chemical or biological substance, or any product thereof, to be studied; a control article means any drug or substance to be studied for the purpose of comparison with the test ariticle.

Article 22 (Test and control article characterization) Before the initiation of a study the testing facility is required to determine and document characteristics of test and control substance such as purity, strength and composition or others.

Documentation by a sponsor or facility on the methods of synthesis, fabrication or derivation of test substance is also required.

A testing facility shall determine the stability of each test and control article before initiation of a study. The label on each storage container for a test or control article must contain the name or code number, the lot number, the expiration date if needed and appropriate storage conditions.

For studies lasting for more than four weeks, a facility shall preserve samples from each lot of test and control articles for the periods specified in the regulaton unless the articles are known to be unstable.

Article 23 (Test and control article handling) Procedures should be established for the handling of test and control articles to assure proper storage, that distribution is effected without contamination or deterioration, that proper labelling is maintained throughout the distribution process, and that documentation exists for the date and quantity of receipts and distributions.

Article 24 (Mixture with carriers) A testing facility shall determine the stability of a test or control article when mixed with a carrier before the initiation of a study, in priciple, and shall also determine the uniformity and concentration of these articles periodically when animal feed is employed as a carrier. If necessary, the expiration date of the mixture shall be indicated on the container.

VII. Protocol for and Conduct of a Study

Article 25 (Protocol) Specific protocols are required for all studies regardless of duration or size. Furthermore, the protocols have to be approved by the management and/or sponsor.

The protocol contains the following informations, but is not necessarily be limited to the following informations:

(1) A title and the purpose of the study.
(2) The name and address of the testing facility and of the sponsor.
(3) The name, address and position title of the study director.
(4) The proposed starting date and duration of the study.
(5) The name, abbreviated name or code number of the test and control articles.
(6) Reason for selection of the test systm.
(7) The species, strain, number, age, sex, body weight range and source of supply of the test system.
(8) The procedure for identification of the test system.
(9) The experimental design and any methods used for the control of bias.
(10) The environmental conditions for the test systems.
(11) The feed. (The description shall include specifications for acceptable levels of contaminants that are expected to be present and are known to be capable of interfering with the purpose or conduct of the study if present above certain levels.)
(12) Solvents and emulsifiers used to dissolve or suspend the test or control article, as well as other materials used as a carrier.
(13) The route of administration of the test and control articles, and the reason for its choice.
(14) The dosage levels of the test and control articles, and the method, frequency and duration of administration, as well as the reason for their choice.
(15) The method by which the degree of absorption of the test and control articles by the test system will be determined, if such is necessary to achieve the objectives of the study.
(16) The type, frequency and method of observations, measurements, tests and analyses to be performed.
(17) Statistical methods to be employed for the analysis of the data.
(18) The records and data to be maintained.
(19) Approval of the protocol by the management (including the sponsor for the study conducted under contract) and the signature or sealing of the study director.

Any revision of the protocol during the course of a study and the reason for the change should be documented and maintained with the protocol by the testing facility. The study director shall sign or seal the amendment, and record the date of such changes in the document.

Aricle 26 (Conduct of a study) The study shall be conducted in accordance with the protocol and SOP under the instruction and supervision of the study director.

The key point in this section is to record the data in indelible ink (except computer input), and is to have data accurately recorded with all changes in raw data made in the form of a signed or sealed and dated amendment which does not

obscure the original entry. Any abnormal or unanticipated phenomenon which occurred during the course of a study should be promptly reported to the study director and documented in detail.

VIII. Reports and Records

Article 27 (Final report) A final report should be prepared for each study and contain the reports of the contributing scientists; it is not necessary to include all the raw data.

The final report shall include and describe the following :

(1) A title and the purpose of the study.
(2) The name and address of the testing facility.
(3) The dates of initiation and completion of the study.
(4) The name, abbreviated name or code number, and lot number of the test and control articles.
(5) Stability of the test and control articles under the conditions of administration.
(6) The species, strain, number, age, sex, body weight range, source of supply, date of receipt and housing conditions of the test system.
(7) The administration route, dosage levels, and method, frequency and duration of administration of the test or control article.
(8) Reason for the choice of dose of the test or control article.
(9) Circumstances that may have affected the reliability of the data.
(10) The type, frequency and methods of observations, measurements, tests and analyses preformed.
(11) Ther name and job assignment of the study director and other scientists engaged in the study.
(12) Statistical methods employed for analyzing the data.
(13) Results of the study, discussion of results and their summary. (Included are dated, signed or sealed reports of each of the individual scientists or other professionals who were involved in the conduct and responsible for evaluations of the report of that study.)
(14) The locations where raw data and specimens are to be stored.
(15) The document prepared and signed or sealed by the quality assurance unit specified under this Standard.
(16) The date when the final report was prepared.

A final report should be signed or sealed and dated by the study director, and any amendment should clearly identify the change being made and reasons for the change should be described with the date of correction or addition.

Article 28 (Storage and retrieval of records and specimens) At the conclusion of a study, all records are to be kept in archives which are accessible to only authorized individuals. The archives are to be properly constructed to minimize the deterioration of contents. Material in the archives shall be indexed by test substance.

When specimens or raw data are retained separately from the archives of the final reports, that storage location should be documented in the archives.

Protocols, specimens, all raw data, other study documentation, and reports should be retained in an orderly fashion to expedite retrieval.

Article 29 (Retention period of records and specimens) Retention of protocols, specimen, raw data, documentation records and final reports are required for the period specified in the Enforcement Regulations of the Pharmaceutical Law.

Specimens which deteriorate markedly during storage, such as histochemical, hematological, teratological and electron microscope preparations, shall be retained as long as the quality of the preparation permits evaluation.

In conclusion, Good Laboratory Practice is intended to promote the quality and validity of test data. It is an auxilliary concept relating to the organizational process and the conditions under which laboratory studies are planned, performed, monitored, recorded and reported.

The application of GLP is of crucial importance to national authorities entrusted with the responsibilities of assessing test data and evaluating chemical hazards. This issue also has an international dimension.

In Japan, the Ministry of Agriculture, Forestry and Fishery and the Ministry of Interational Trade and Industry have established GLP's for testing agricultural chemicals and environmental chemicals, respectively; these will be implemented in the near future.

The FDA's adoption of GLP regulations in 1978 stimulated consideration of GLP in the United States Environmental Protection Agency, in other countries and in international organization Agency, in other countries and in international organizations such as OECD and WHO, and proposals of GLP's have been made or being established.

GLP regulations or standards will increase public confidence in decision making by regulatory authorities and will increase assurance that safe pharmaceuticals and other chemical products are approved for marketing. Furthermore, the evaluation of recent laboratory inspections in Japan reveals that the GLP Standard represents an achievable goal which is being adopted by the regulated laboratories and industries.

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