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Review

Good Laboratory Practice Requirements in Oriental Pharmacy

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ABSTRACT

Good Laboratory Practice(GLP) is becoming more and more important in the research and development of Oriental Pharmacy(OP) and its globalization. If a OP product is to be registered as Over-the-Counter(OTC) drug and enter international markets, the safety and efficacy studies conducted according to GLP requirements is necessary. The article introduces the content of GLP requirements and the recent development of GLP. The safety and efficacy assessment for OP or herbal medicines under GLP are also covered. This paper also briefly describes the areas that should be covered by GLP regulation and the areas that do not need to follow GLP requirements.

Key words : Good Laboratory Practice(GLP); Oriental Pharmacy(OP); Herbal Medicine; Safety and Efficacy; Quality Control.

Introduction

Laboratory tests are essential for drug development. They provide the screening requirements to rule out toxicity, the conformation for quality, the bioassay for adverse effects and drug interaction, and other specific steps towards chemical analysis and development.

Good Laboratory Practice(GLP) is a quality system concerned with the organizational process and the conditions under which non-clinical quality and safety studies for drugs, food additives, agricultural chemicals, chemicals and cosmetics are planned, performed, monitored, recorded, archived and reported in the laboratory. The ultimate purpose of GLP regulation is intended to assure that non-clinical laboratory study data are of high

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quality, integrity and reliability.

The results of pre-clinical laboratory studies determine whether a new preparation is appropriate to undergo clinical studies of if it has to undergo further development. To maintain a high quality pre-clinical study, the whole study processes must meet all requirements of GLP. Since the USA issued its first GLP guideline in 1978 (Liu et al., 2000; Liang and Huang, 2000), it has since been adopted by many other countries. Since then, many countries had launched their own GLP Guidelines (Harston et al., 1994).

Background of GLP

In the 1970s, fraud practices were quite common in the research of agricultural chemicals and drugs in the world. This aroused much caused public concern in the USA (Liang and Huang, 2000; FDA, 1997). In order to stop such dangerous practice in health care product research, the US Food and Drug Administration(FDA) issued a regulation, which was based on the US Public Health Service Act(PHSA), to guided the non-clinical laboratory studies. The drug manufacturers must demonstrate the efficacy and safety of the drugs in the laboratory before they could be tested on humans(Tian, 2001). The current GLP guideline was developed from the US Regulation. During the ten years of GLP implementation, FDA inspected their research institutes located domestically and abroad a total of 690 times. The results of any study should be repeatable, wherever the study was conducted, at any time and by any operators. The investigations did indicate that if a research were conducted according to GLP, the results obtained in different organizations and at different countries and regions, should be comparable(Turnheim, 1993).

GLP in the World

As the basic principles and requirements of GLP in different countries are quite similar, testing data may be exchanged freely internationally. In fact, the US FDA has reached an agreement with the United Kingdom, the Federal Republic of Germany, France, Switzerland, Italy, Japan, Sweden and Netherlands for a mutual acceptance of laboratory data. Cross acceptance of data eliminates duplications of laboratory procedures(Turnheim, 1993; OECD; UK Department of Health, 1992; Taiwan Health Administration, 2000).

In 1989, a round table meeting was held in the USA for GLP evaluation. During the meeting, all participants coming from relevant countries agreed on the absolute value of GLP for the safety assessment of healthcare product. The GLP guidelines therefore were internationally endorsed.

Safety and Efficacy Assessment of Oriental Pharmacy

Today, many herbal remedies are being used prophylactically to maintain or enhance good health or prevent certain conditions from occurring. The World Health Organization (WHO) estimates that four billion people - 80% of the world population - use herbal medicine for some aspects of primary healthcare(Farnsworth et al., 1985).

Written records about medicinal plants dated back at least 5000 years to the Sumerians (Swerdlow,

2000). Since the early 19th century, attempts have been made to understand the actions and properties of OP through scientific research.

Herbs are natural products and thus do not have a consistent, standardized composition. Herbs contain numerous chemical constituents (up to several hundred in some cases). Different parts of the plant (e.g. roots, leaves) contain a different profile of constituents. Furthermore, the content and concentration of the constituents can be influenced by climate, growing conditions, time of harvesting and post-harvesting treatment. If a OP medication can be proofed for its safety and efficacy as well as its batch-to-batch and manufacture-to -manufacture consistency, it is possible to be registered as an OTC drug in the US or Europe markets. GLP is one of the most important requirements in drug development, which is usually required in drug safety and efficacy study. Implementation of GLP requirements will increase the costs by about 20% (Fleischhauer, 1984); the cost is used for quality control, documentation (e.g. SOPs) and archiving and analysis of reagents and test samples. For example, in the US, the cost of Ames test (a test for determining of a chemical is a mutagen) conducted by a GLP laboratory is around 4500-6000 USD; if conduced according to non-GLP standard at same laboratory, the cost is only 800-1600 USD (Fu, 2002). So some GLP laboratories of international pharmaceutical companies have two systems: GLP standard research and non-GLP standard research. Only research intended for registration are performed according to GLP requirements (Fu, 2002). From the general recognised principles of GLP, safety evaluations usually include single dose toxicity test, repeated dose toxicity test, foetal development toxicity test, reproductive toxicity test, mutagenicity test and carcinogenicity test (Harston et al., 1994).

Opinions about the safety, efficacy, and appropriateness of medicinal herbs vary widely among medical and health professionals in countries where herbal remedies are used. Some countries' professionals accept historical, empirical evidence as the only necessary criterion for herbal medicine's efficacy. Others would ban all herbal remedies as dangerous or of questionable value.

Main Contents and Requirements of GLP

GLP regulations usually cover the following types of studies: non-clinical studies; safety studies, and studies in support of an application for a research or marketing permit. In administrative practices, GLP should include: facility organisation; facilities; equipment maintenance; personnel and training; animal care; record keeping; reporting; and quality assurance. However, GLP regulations do not cover scientific practices, such as: protocol design; testing methods; types of equipment; personnel qualification; animal selection; or data interpretation.

The following are the main contents of GLP regulations;

(1) Personnel(Wang, 2001a)

According to GLP guidelines, the study team should include a Study Director, a Principal Investigator, Study and Quality Assurance Personnel.

The Study Director should be a toxicologist with many years of experience. He is the focal point of study control and has the responsibility for the

overall conduct of the study and for its final report. The Principal Investigator should have the ability to ensure that the delegated phases of the study are conducted in accordance with the applicable principles of GLP.

All personnel involved in the conduct of the study must be knowledgeable in the principles of GLP, which are applicable to their involvement in the study. The Quality Assurance Personnel are independent of the study and assure test facility management of compliance with these principles of GLP.

(2) Test facility(Wang, 200lb)

The basic facilities for a GLP lab should include animal raising and housing apparatus, equipment for testing various functional para-meters, storage facilities for study supplies and test medication preparation equipment, as well as washing and disinfecting apparatus. Among them, animal housing and relative equipment are critical for a GLP lab because they are the core of safety assessment. In addition to controlling the timing of the tests, advanced and automatic apparatus ensure that the test results are accurate, objective and reliable.

(3) Standard Operating Procedures(Li, 2003)

Standard Operating Procedures (SOPs) mean documented procedures, which describe how to perform tests or activities normally not specified in detail in study plans of test guidelines. SOPs are very important for GLP implementation because it makes the test result accurate, comparative, authentic and repeatable. In order to avoid the deviation of the test result such as "fault positive" or "fault negative", each step of operating procedure of a safety assessment study must follow the unified guideline that is SOP, including: the requirements for receipt, identification, labelling, handling and storage of the test medication; the requirements for experimental animals of reservation, acceptance, weighing, health examination, antiscolic, animal selection criteria, animal raising procedures, nutritional standard, drinking water hygienic standard, animal room clearing and disinfecting standards and dead animal treatment procedures; various calculating formulas for test medication preparation and administration; apparatus maintenance, cleaning and calibration; the requirements for testing observation record procedures, data treatment, storage and archive; the requirement for specimens in sampling, handling and treating; procedures of lab supplies purchasing, storage and getting for use; the requirement for the moving route of staff, study material and animals; and the requirements for experimental data collection, summary of results, calculations and determinations of statistical significance and final report writing.

(4) Management (Kang, 2003)

Apart from equipping with advanced facilities/ equipment, the establishment of a rigorous control system is also important. The system should include: the project research management; animal raising and environmental monitoring; reagents and apparatus management; specimen of test medications and biological material handling; SOPs management; and archive management for all test data including study plans, raw data, final reports.

The heart of GLP regulation implementation is reflected in its Quality Assurance Program. The main responsibility of Quality Assurance Program

are to: prepare the study schedule; inspect the study plans; conduct the inspections during the study in progress, which include study-based inspections, facility-based inspections and process-based inspections; prepare quality Assurance document; inspect the study results and the reports; inspect the qualification of study personnel; inspect the documents for submission; and inspect the study plans and SOPs being followed.

GLP Laboratory Establishment

(1) Hardware

The general GLP requirements for test facilities are making sure the data and the results obtained should be reliable and the quality management system should be maintained and monitored according to GLP standards (Wang, 2001b). The following aspects are essential: animal housing facility; apparatus for various parameters testing; sufficient storage and supply facilities; test medications handling, washing and disinfecting facilities; and archive facility.

To build up a GLP laboratory that meet all international requirements would require an area of 3000-4000 square metres and cost about 30-40 million RMB(Yuan and Lu, 1999). The construction of Shanghai New Drugs Safety Evaluation Centre has been completed and investment of 50 million RMB was estimated (Ye, 1997).

(2) Software

Construction of hardware of a GLP laboratory is relative simple, but construction and following the software according to GLP requirements is not easy (Guo et al., 2003). The overall principles of GLP is assure that data obtained are a true reflection of the results obtained during the study and can therefore be relied upon when making risk/safety assessments(UK GLP MA). In order to achieve the goal, the following aspects should be carried out: preparation of the study personnel training programme formulation of a series Standard Operating Procedures; and formulation a set of rigorous Quality Assurance Program.

Conclusion

All herbal products including OP when supplied, as medications, should be regulated for safety, quality and for appropriate evidence of efficacy. The purpose of Good Laboratory Practice is to promote the quality of drug research and development. In the future, OP products should be strictly studied to prove safety and efficacy, according to GLP requirements. The quality of test data under the GLP regulations is the basis for the mutual acceptance of data among different countries. If individual countries can rely on test data developed independently with confidence, duplicated testings can be avoided, thereby saving time and resources.

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