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Quality of animals in GLP studies

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Abstract

GLP is 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, reported and archived. The purpose of studies on "non-clinical health and environmental safety" is to investigate the physical/chemical, biological and/or toxicological properties of the test item under investigation. The GLP principles are not only concerned about the possibility for checking back the identity of the test item but also ensures that the correct test item has been applied to the test systems. Test system characterization is an important quality control criterion in GLP studies. Regulators need sound, healthy, valid, unbiased test systems, to obtain reproducible, repeatable and reliable test results. This is possible only when we use properly characterized, pure, healthy test systems at a globally harmonized environmental conditions.

Key words: GLP studies, test systems, genetic monitoring, microbial monitoring, parasites monitoring

Introduction

United States Food and Drug Administration (USFDA) found that several reports on animal toxicity studies were unreliable, during 1970. The investigations of the USFDA in several toxicology laboratories demonstrated that, a lack of organizational and poor management practices. This prompted the United States to introduce some regulations in the conduct of regulatory toxicology studies. Consequently Good Laboratory Practice (GLP) regulations came into existence in 1978. The Organization for Economic Co-operation and Development (OECD) principles of GLP were first developed by an expert group on GLP established in 1978 under the special programme on the control of chemicals. The GLP regulations for non-clinical laboratory studies published by the US FDA in 1976 provided the basis for the work of this expert group. The OECD Council formally recommended these principles of GLP for use in OECD Member Countries in 1981, and adherence to these principles permits international acceptability of safety testing data from different countries (Mohanan, 2006).

Good Laboratory Practice (GLP) is 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, reported and archived. In India, the National GLP Compliance Monitoring Authority (NGCMA) was notified in the Gazette of India, on August, 31st, 2002. The NGCMA has adopted

the OECD Principles of GLP. India attained Full Adherent Status on Mutual Acceptance of Data (MAD) in OECD on March 3, 2011. The Principles of GLP should be applied to the non-clinical safety testing of test items contained in pharmaceuticals, pesticides, cosmetic products, veterinary drugs as well as food additives, feed additives and industrial chemicals. The test items are frequently synthetic chemicals, but may also be of natural or biological origin and in some circumstances, living organisms. The purpose of studies on "non-clinical human health and environmental safety" is to investigate the physical/chemical, biological and/or toxicological properties of the test item under investigation. The GLP do not concern the scientific or technical content of the research programmes or study, however emphasize on precise documentation and other standards (Saha, 2006).

GLP regulates all non-clinical safety studies that support or are intended to support applications for marketing permits for new chemical entities (industrial chemicals, pharmaceuticals, cosmetics, veterinary drugs, nutrition supplements for livestock, and biological products), to be submitted to the regulatory authorities of different countries. The role of GLP compliance is not to regulate safety directly because that is the responsibility of regulatory authorities such as the Drug Controller General of India and Food and drug Administration of USA. Regulatory authorities continuously work to determine the level of risks acceptable to the society and elaborate on scientific inputs and technical data to ensure that risks do not exceed the contemplated level of risks. It is a complex exercise and needs to be performed with out any break. GLP is one of the links in this long chain of activities to ensure safety and addresses non-clinical studies (USEPA, 1993; OECD 1997; USFDA 1993).

The GLP principles are not only concerned about the possibility for checking back the identity of the test item but also ensures that the correct test item has been applied to the test systems. Test system in GLP is slightly a complex name and is generally considered as the animal subject. Test system in GLP also applies to such subjects as equipments (physico-chemical), ground water, soil, insects, earthworms, honey bees and microorganisms such as daphnia. Proper storage, housing, care and handling of biological test systems should be ensured for generation of quality data. Isolation of newly received animal and plant test systems till confirmed to be free from ill health would be carried out. Diagnosis and treatment of diseases would be documented during the studies. Similarly the source, arrival date and arrival conditions of the test systems would be documented. Appropriate information for the proper identification of the test systems must be written on their cages (Schwenk *et al*. 2002).

Test systems in GLP

Followings are the test systems generally used in GLP studies.
Test system in studies on chemicals are

- Mammals (rodents, non-rodents)
- Fish
- Algae, Daphnids, Fruit flies
- Human skin, Cow's eyes
- Bacteria, Viruses, Fungi
- Mammalian cell lines
- Soil and (Sea-) water

Test system in pesticide studies are

- Crops (annual, multi-annual)
- Soil, Air
- Ecosystems

Test system in veterinary drug studies are

- Cattle
- Poultry

The quality of test systems (animals) in OECD Principles of GLP requires its

1. Species / Strain
2. Health status
3. Supplier (compliance status)
4. Background data
5. Separation

In GLP studies, it is the responsibility of the study director to match the quantity and quality of test systems in study requirements. The Study Director must define the

- phenotype / genotype
- sex, age
- number and
- reasons for choice (justification)

There should be a proper established and maintained conditions for the

- Storage
- Housing
- Handling and
- Care of test systems.

It is also recommended that there should be an established mechanism for the

- isolation till health status has been evaluated
- do not use test system, when unusual mortality/morbidity occurs
- at experimental starting date test system must be free of any disease or condition that might interfere with study purpose
- isolate and treat test systems that become diseased or injured
- keep records of disease and treatment
- keep records of source
  - date of arrival
  - arrival condition
  - acclimatise to test conditions for adequate period of time

It is the responsibility of the management to procure these test systems from reputed / standard suppliers who can guarantee with the certificate on the strain, quality, characterization etc. The Test facility management make sure that the availability of animal/experimental rooms, environmental conditions such as temperature, humidity, air cycle, light, manpower, equipment, support services like pathology, preparation of study plans, SOPs, animal procurement, health surveillance and quarantine (if procured from outside the country). Preparation of data acquisition forms, conduct of pre-study measurements on study animals to set baseline rates of body weight gain, clinical chemistry values.

Test system characterization

Regulators need sound, healthy, valid, unbiased test systems, to obtain reproducible, repeatable and reliable test results. Test system characterization is an important quality control

criterion in GLP studies. There are mainly three types of test system (animals) characterizations

1. Genetic Monitoring.
2. Microbial monitoring and
3. Parasites monitoring

The major function of any genetic monitoring is to either monitor the genetic integrity of inbred strains or variety of the mutant alleles in the mutant stock. Good genetic quality can be ensured if genetic monitoring is done. The genetic monitoring can be done with skin grafting, biochemical markers, hemagglutination, RFLP (Restriction fragment length polymorphism), SSLP (Single sequence length polymorphism) and SNP (Single nucleotide polymorphism).

The microbial monitoring is another quality check practiced all over the world. Like all living organisms, the laboratory animals also carry both parasitic and saprophytic microorganisms. A well qualified test system (animals) will be a germfree, pathogen-free or specific pathogen free. Some of the microbial quality check includes, the evaluation of

- LCM virus
- *Mycoplasma pulmonis*
- *Klebsiella pneumoniae*
- *Staphylococcus aureus*
- Salmonella spp.
- *Streptococcus pneumoniae*
- *Pasteurella pneumotropica*
- Sendai virus
- Mouse encephalomyelitis virus
- H-1 virus

It is also important to understand the diseases of zoonotic importance while working with animals and avoid exposure to the microbial pathogens.

Parasites monitoring: It was well documented that several parasites that affect the laboratory animals. There are two types of parasites; ecto and endo parasites. This can be monitored in blood or faecal matters (endo). When animals are infected with parasites, there are changes in the clinical and pathological conditions, which lead to false interpretations of the study results. Parasites are to be monitored to avoid such type of misinterpretations in animal experiments.

Facilities for housing test systems and for carrying out studies are checked for their adequacy. It is mandatory that, all records of source, date of arrival and arrival conditions of animals, quarantine for newly received animals and health certificates of animals are to be documented (USFDA, 1978; Shillam, 1979; ICH, 1997; Dent, 2006).

Apart from the health certificate received from the Veterinary Professional, it is also one of the responsibilities of the study director, to have criteria for acceptance of the test system (user qualification) for the proposed study. Following parameters may be considered for the above criteria (Table 1).

Table 1: User qualification (Justification for healthy animals) for laboratory animals before experiment

Species :								Date.
Parameters	Animal Nos. / ID							
Adult								
Weight								
Sex								
Pregnancy (checking abdomen)								
Nasal discharge								
Lacrimation								
Circling								
Hair								
Animal movement								
Checking of eyes								
Ears								
Genital organs								
Ectoparasites								
Forelimbs								
Hind limbs								
Blood parameters*	colony checking							
Clinical biochemistry*	colony checking							
Faecal analysis*	colony checking							
Health status	Good/suitable for experiment					Signature: SD		
	Not suitable for experiment					Date:		

N: Normal; A : Abnormal; NL : Nil; NP : Not Pregnant; Animal received by :
*Parameters evaluated by every 6 months (colony checking)

Conclusions

In the context of globalization, these studies are global and for the global market. The scientific and safety information generated needs to be applied world wide and hence the activities should be of uniform international quality standard. GLP makes this possible, since it assures quality and integrity of the data used for regulatory purpose. This is possible only when we use properly characterized, pure, healthy test systems at a globally harmonized environmental conditions.

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