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TOXICOLOGY RESEARCH LABORATORY

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REPUBLIC OF KOREA

Technical Report: General Toxicology*

Prepared for the Government of the Republic of Korea
by the United Nations Industrial Development Organization,
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Person I met in Seoul:

26 Oct. 1987

Mr. Park, Pyoun Chol., Programme Officer
United Nations Development
Programme in Korea

Persons I met in Taejeon(KRICT):

23 Oct. 1987 and 3 Dec. 1987

Jung Koo Roh, Ph.D., Director of Toxicology Research Center, KRICT

Sang Seop Han, Ph.D., Senior research scientist of Toxicology Research Center, KRICT

Content

1. Introduction

Following the first trip to Korea Research Institute of Chemical Technology (KRICT), Republic of Korea, in April, 1987, I visited the institute again as mission of UNIDO on October 18 - November 1 and November 22 - December 7, 1987. I gave advice and established documents of Standard Operating Procedures (SOPs) for toxicity studies which meet international requirements such as Good Laboratory Practices(GLPs). The institute staff required me as follows:

(1) To advise in preparing Standard Operating Procedures to meet GLP.

(2) To assist in designing and conducting toxicity studies through oral, dermal and especially in clinical observations during these studies.

(3) To assist in finalization and interpretation of study data and review the work program and define the requirements of special training for toxicity studies.

(4) Recommendation

My work for above 4 items proceeded satisfactorily. This report describes this work consultation in Toxicology Research Center of KRICT.

2. Preparation of Standard Operating Procedures(SOPs)

The SOPs for toxicity studies were prepared in accordance with KRICT's requirements.

2.1 Items of KRICT's requirements

(1) Receipt, labelling and storage of test and control articles and method of mixing with carriers.

(2) Animal room preparation and animal care.

(3) Maintenance and repair of facilities and equipment.

(4) Identification, housing, placement and trasfer of animal.

(5) Observation on animals, such as general signs.

(6) Methods of measurement, laboratory tests and analyses.

(7) Handling of moribund or dead animals.

(8) Necropsy or postmortem examination of animals.

(9) Collection and identification of specimens.

(10) Histopathological examinations.

(11) Data handling, storage and retrieval.

2.2 Kinds of SOPs

The standard operating prodedures(SOPs) meet which international requirements were established. The details such as the numbers of SOPs and contents are described in items 2.3 and 2.4. Total numbers of SOPs which I prepared are 451.

A. SOPs for general toxicity studies

1) General toxicity studies in rodents: GTR .....(22)

2) General toxicity studies in non-rodent(dog): GTN.....(31)

3) General toxicity studies in non-rodents(monkey and cat): GTN.....(29)

4) Acute toxicity studies: ACU.....(11)

5) Haematological examinations: HEM.....(11)

6) Blood chemical analyses: BIO.....(34)

7) Histopathological examinations: PAT.....(17)

B. SOPs for others

1) Laboratory animal husbandry in toxicity studies: ANI.....(104)

2) Maintenance and calibration of equipment: MAI.....(38)

3) Test and control articles: SAM.....(5)

4) Retention of GLP substance test, compound and specimens: DOC.....(9)

5) Reproduction studies: RER and REN..... .....(92)

6) Local irritation studies: LOC.....(42)

7) Maintenance of animal facilities.....(1)

8) Others:OTH.....(5)

I prepared model SOPs for toxicity studies and laboratory animal facilities and then arranged those to adopt to these facilities and administrative system in Toxicology Research Center of KRICT. These SOPs written in Japanese are being translated to Korean by KRICT staffs at present.

2.3 Contents of SOPs for general toxicity studies

Contents of SOPs for general toxicity studies in rodents, dogs, monkeys, and cats, and these for acute toxicity studies were shown as fellows;

A. Content of SOPs for general toxicity studies in rodents(GTR)

1) Preparation of protocols

2) Animal acclimation and selection

3) Random allocation of rodents to groups, cages and racks

4) Test and control articles handling

5) Test and control articles formulation

6) Administration of prepared test and control articles

7) Observation of rodents

8) Handling of animals found moribund or dead during study

9) Animal weighing

10) Preparation for a test article to be mixed with a carrier, and measurement and calculation of food consumption

11) Calculation of actual dietary intake of a test article in deitary toxicity study

12) Urine collection

13) Measurement of water intake and urine volume

14) Examination of fundus

15) Blood sampling

16) Measurement of organ weights

17) Procedures of necropsy

18) Data handling, storage and retrieval

19) Amendment and approval of data and tabling

20) To deal with accidental

21) To operate the computer to be collected data of body weights and food consumptions

22) Animal receipt

B. Content of SOPs for general toxicity studies in dogs(GTN)

1) Preparation of a study

2) Preparation of a protocol

3) Pre-experimental acceptance testing in dogs

4) Random allocation of dogs to groups

5) Instructions for tattoing dogs with identification numbers

6) Test and control articles formulation

7) Administration of prepared test and control articles

8) Observation for clinical signs

9) Animal weighing

10) Measurement and calculation of food consumption

11) Measurement of body temperature

12) Measurement of heart rates

13) Urinalyses

14) Ophtalmoscopic examinations

15) Blood sampling

16) Prothrombin time estimation

17) Recording of electrocardiograms(ECGs)

18) Measurement of water intake and urine volume

19) Collection of blood, urine, feces and organ samples for estimation of content levels of a test article

20) Procedures of necropsy

21) Measurement of organ weights

22) Animal handling

23) Abnormal animal handling

24) Random allocation of animals to housing

25) Procedures for holiday

26) Procedures for accidents

27) Procedures of washing and sterilization for cage, rack and others

28) Data handling, storage and retrieval

29) Bleeding time estimation

30) Animal management on study

31) Test and control articles handling

C. Content of SOPs for general toxicity studies in monkeys and cats(GTN)

1) Preparation of studies

2) Preparation of protocols

3) Monkey, animal handling

4) Pre-experimental acceptance testing

5) Random allocation of animals to groups

6) Instructions for tattoing animals with identification numbers

7) Procedures of washing and sterilization for cages, racks and others

8) Test and control artticles formulation

9) Administration of prepared test and conrtol artilces

10) Observation for clinical signs

11) Animal weighing

12) Measurement and calculation of food consumption

13) Measurement of body temperature

14) Measurement of heart rates

15) Urinalyses

16) Ophtalmoscopic exaamination

17) Blood sampling

18) Prothrombin time estimation

19) Collection of blood, urine, feces and organ samples for estimation of content level of a test article

20) Procedures of necropsy

21) Measurement of organ weights

22) Abnormal animal handling

23) Procedures for holidays

24) Procedures for accidents

25) General record handling procedures

26) Random allocation of animals to housing

27) Animal management on a study

28) Test and articles handling

29) Study procedures in cats

D. Content of SOPs for acute toxicty studies(ACU)

1) Animal acclimation and selection

2) Test article handling

3) Test article formulation

4) Pre-experimental acceptance

5) Administration of a prepared test article

6) Observation of behaviors

7) Procedures of necropsy

8) Calculation of LD 50 values by probit analyses

9) Data handling, storage and retrieval

10) Preparation of protocols

2.4 Contents of SOPs for laboratory animal husbandry

Contents of SOPs for laboratory animal husbandry in toxicity studies on 7 species of animals were shown below.

A. Housing

1) Caging or housing system for laboratory animals

2) Social environment

3) Space recommendations for laboratory animal activity

4) Animal environment in laboratory animal rooms

a) Micro-and macroenvironments

b) Temperature and humidity

c) Ventilation

d) Illumination

e) Noise

5) Food

6) Bedding

7) Water

8) Sanitaion

a) Cleanliness

b) Waste disposal

c) Vermin

9) Identification and records

10) Emergency, weekend, and holiday care

B. Venterinary Care

1) Preventive medication

2) Animal procurement

3) Quaranine and stabilization

4) Separation by species, source and health status

5) Separation to avoid interspecies disease transmission

6) Separation by source or microbiological status

7) Surveillance, diagnosis, treatment, and control of disease

8) Anesthesia and analgesia

9) Surgery and postsusrgical care

10) Euthanasia

The SOPs were also established for acute, subacute and chronic toxicity studies, reproduction, and local irritation studies, which meet international requirements. I am sure, that these will be of great help fo rToxicology Research Center of KRICT to conduct toxicity studies in accordance with GLPs.

In addition, SOPs for the dependency, antigenicity, mutagenicity and carcinogenicity studies should be established, which are essential for the new drug application. Of course these SOPs should meet GLPs.

3. Summary of Advice

3.1 Advice for preparing protocols of toxicity studies

A protocol shall be approved by the management and the study director. The protocol clearly indicates the objective and all methods for the conduct of the toxicity study. Each study shall have a written protocol which contain the following information:

1) A descriptive title and statments 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 sponser and the name and address of the testing facility at which the study is being conducted.

4) The proposed starting and completion dates.

5) Justification for selection of the animals.

6) Where applicable, the number, body weight range, sex, source of supply, species, strain, and age of the animals.

7) The procedure for identification of the animals.

8) A description of the exprimental design.

9) 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.

10) The route of administration and the reason for its choice.

11) Each dosage level, expressed in milligrams per kilogram of body weight or other appropriate units, of the test or control article to be administrated and the method and frequency of administraton.

12) Method by which the degree of absorption of the test and control articles by the test system will be determined if necessary to achieve the objectives of the study.

13) The type and frequency of tests, analyses, and measurements to be made.

14) The records to be maintained.

3.2 Instruction for clinical observations during the toxicity studies

Concering oral and dermal toxicity studies, I instructed KRICT staffs using Irwin's method (Irwin, S., Psychopharmacologia, 13, 222, 1968). I gave some data sheets and 5 reference information to them.

3.3 Advice for evaluation of study data and preparation of final reports

I gave them advice about finalization and interpretation of study data, and review of the work program concerning subacute and chronic toxicity studies which are being conducted at KRICT. Ten reference documents regarding preparation of final reports which meet GLPs'requirements were handed to them.

4. Recommendation

4.1 Future preparation of SOPs

KRICT staffs have been conducting acute, subacute and chronic toxicity studies in Rodents B.S. facilities of Toxicology Research Center. Now, they are making efforts to level up their technique.

As I worte, I have established 451 SOPs to meet GLPs during stay in KRICT. I expect SOPs for future studies should be prepared on the basis of the protocols I made.

4.2 Environmental control of animal facilities

I gave some advice to KRICT staffs for environmental maintenance and management of using rodent facilities and non-rodent facilities under construction. Safety procedure for workers and preventive medication for laboratory animals are pressing problems. The folloving are our recommentation:

a. To clarify a clean zone in testing facilities

b. To set wet shower room for workers

c. To establish methods of sterilization and preparation of a test article in dietary administration

d. To furnish necessary equipment

e. To be noise-proofed in working rooms

f. To improve the methods of disposal of waste materials