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TOXICOLOGY RESEARCH LABORATORY

DP/ROK/82/028

REPUBLIC OF KOREA

Technical report: General Toxicology*

Prepared for the Government of the Republic of Korea
by the United Nations Industrial Development Organization,
acting as executing agency for the United Nations Development Programme

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EXPLANATORY NOTES

Abbreviations

KRICT - KOREA RESEARCH INSTITUTE OF CHEMICAL TECHNOLOGY

GLP - GOOD LABORATORY PRACTICE

SOPS - STANDARD OPERATING PROCEDURES

UNDP - UNITED NATIONS DEVELOPMENT PROGRAMME

ABSTRACT

This mission forms part of the expert assistance provided for the KRICT Toxicology Research Center in general toxicology as job DP/ROK/82/028/11-59/32. I.G. It was undertaken between 15th January and 24th February 1987.

The main objective was to guide the staff of the Center towards a fuller understanding of toxicological principles and strategies, to improve the quality and range of experimental techniques available to them and to help them to move towards conforming to GLP standards acceptable to International Regulatory Agencies.

The staff were given guidance in the form of lectures, seminars, informal discussions, written material and samples. Recommendations were made on equipment and on future training by visiting experts and by sending Research Center staff abroad.

CONTENTS

INTRODUCTION

This report covers a mission of one month, commencing 15th January 1987, during which 23 days were spent at the KRICT Toxicology Research Center. This Center, established with UNDP aid and guidance. is intended to develop as the main facility for Contract Toxicology in the Republic of Korea. To achieve this goal it is necessary to develop expertise in general toxicology to a standard acceptable to Regulatory Authorities Worldwide. This mission aimed to provide advice, guidance and training which would further the developemnt of the Research Center and its staff.

The objective of the mission was to work closely with the Director of the Center(Dr. Roh) and his staff to provide assistance in the planning, operation and administration of short term and long term animal experiments and specifically to :

1. Advise on the design of protocols for acute, sub chronic and chronic toxicity tests ;
2. Train the veterinarians for the assessment of animal quality and gross signs of diseases during guarantine period, ;
3. Instruct and train the staff of Toxicology Center in
   a) Observation of clinical signs during tests
   b) Procedures and evaluation of gross necropsy and histopathology ;
4. Advise in experimental data processing and evaluation of safety limits.

Following briefings with United Nations staff and with Dr. Roh and his senior staff these objectives were redefined as :

1. Advise on the design and conduct of repeated dose animal studies.
2. Train veterinarian and other staff in a variety of practical techniques and review current methodology.
3. Advise on further training requirements and consultants including those for pharmacology.
4. Review the existing and planned equipment and advise on future needs.
5. Advise on GLP compliance and assist in the preparation of further Standard Operating Procedures.

These objectives were achieved through individual discussion, practical seminars,and formal lectures as is described more fully later in this report.

RECOMMENDATIONS

1. The centre should broaden its experience of long term animal studies to include other routes of administration and other species.
2. Compliance with GLP should be a high priority objective for the center.
3. The training programme should continue with consultant experts and overseas training.

I. OBJECTIVES

The intention of this mission was to provide advice and assistance which would develop the understanding and practical expertise required to enable the Research Center to conduct general toxicological studies to internationally acceptable standards.

The Research Center has progressed rapidly since its foundation but many areas of general toxicology have yet to be developed. Currently long term gavage studies are not undertaken and it was felt that practical advice was needed on the various routes of administration. Some other experimental methods in rodents have to be developed.

As it stands at present the Research Center could not reach the GLP standards required by International Regulatory Authorities and some SOPS were lacking or inadequate.

At present studies in dogs cannot be undertaken. A suitable facility is now under construction and therefore it was necessary to advise on the principles and methodology of dog studies and the equipment which will be necessary for such work.

The Research Center plans to undertake a substantial programme of pharmacodynamic evaluation and there was a need to identify consultants for this type of work.

II ACTIONS

The general and specific objectives which were established were addressed by various actions which fell into a number of categories. These are discussed under the following headings :

A Informal Discussions

B Lectures

C Seminars

D Documentation

E Equipment

F Training Requirements

A. Informal Discussions

These contributions took place on an ad hoc basis whenever staff had any specific questions to discuss. Some time was spent in various laboratories and animal areas looking at procedues and making suggestions where appropriate.

B. Lectures

Seven lectures were given to senior staff. Most of these used overhead projection material prepared on site and copies were made availabl in advance to those attending the presentations. Comprehension was high. The material was presented informally to encourage discussion. Titles were as follows :

January 28th — How do we decide doses for long term experiments?

The potential use of the compound had first to be defined since for pharmaceuticals, food additives, biocides, etc different criteria would be used. The route of administration, physical and chemical properties, pharmacodynamic, pharmacokinetic and metabolic data were important and for pharmaceuticals human data were needed. Acute and dose ranging toxicity data were discussed. The necessity to identify the toxicity by the use of very high doses was emphasised.

February 2nd — Choice of Species and routes of adminstration

This followed logically from the preceding lecture. The need for a non-rodent was explained and the pros and cons of various non-rodents were reviewed. The methodology of the use of various routes of administation was discussed.

February 4th — Experimental procedures in lief : collection of body fluids : tests to be performed

This reviewed the theory and practice of the various clinical and laboratory studies carried out on the animls during the in life phase of a study.

February 6th — Protocols and standard operating procedures : satisfying International Regulatory Requirements

The importance of Standard Operating Procedures and protocols in GLP compliance was emphasised as was the need for full documentation and archiving of data. The role of the Study Director was discussed. Copies of over 400 SOPS were made available to staff in various sections of the Center to be used as a basis for SOP design when appropriate. Copies of the OECD guidelines and of reviews of regulatory requirements for Japan, USA and Europe were also provided.

February 10th — The use of dogs in toxicology : Requirements and problems

Since next year the Center will be able to conduct dog studies this lecture was presented to provide informtion on study design, procedures, equipment and practical requirements for dog studies.

February 11th — Pharmacological toxicology

This lecture reviewed the methods available for studying the pharmacodynamics of novel compounds as part of their toxicological evaluation.

February 12th — The philosophy and policies of toxicological testing of drugs

This final lecture was intended to present an overall review of our principles and objectives in the toxicological study of potential drugs.

C. SEMINARS

Practical seminars were held in the laboratories to present various methodological improvements in dosing and in-life techniques and to review current procedures including clinical observations and necropsies.

D. DOCUMENTATION

Copies of over 400 Standard operating Procedures were providec as were reviews of guidelines for Japan, USA and Europe. The OECD guidelines were also supplied. All overhead projector material prepared for the lectures was copied and distributed in advance to those attending the lectures.

E. EQUIPMENT

A critical review of existing equipment and of the equipment proposed for purchase was undertaken. Several planned items were considered unnecessary or not cost effective. Some additional apparatus was recommended particularly for use in the dog facility and for undertaking pharmacodynamic studies and pharmacological screening. Makes and models and suppliers names were provided whenever possible. Samples of various dosing needles and catheters were provided.

F. TRAINING

The two aspects of training were discussed, consultants and secondment of staff to laboratories overseas. Consultants were considered to be urgently necessary in at least two areas where suggestions could be made of experts who would be willing to act as conultants these were :

GENERAL AND CARDIOVASCULAR PHARMACOLOGIST

D.F. Weetman

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Dr. Weetman has been a pharmacologist in industry and academia for over 20 years. He is on the Executive Committee of the British Pharmacological Society and is an editor of the British Journal of Pharmacology. He is a consultant in pharmacology to several European Pharmaceutical companies.

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It was felt that much of what was needed to further the training of the toxicologists at the Research Center was an expert in the technology of toxicology rather than a scientist who would be less familiar and less expert with animal techniques on a day to day basis. Mr. Conybeare has been a technician in toxicology for 21 years and has an exceptional range and depth of practical skills. He is a Fellow of the Institute of Animal Technicians and a Member of the Institute of Biology. He holds a Higher National Diploma in Applied Biology and has been an invited lecturer in the USA Israel and Scandanavia as well as in the UK.

The other aspect of training by sending staff to laboratories aboroad was also considered. Several staff at the Center working in general toxicology understand sufficient English to benefit greatly from such an opportunity. This is particularly true in some specialised technical areas where spending time in a laboratory where a wide range of equipment, skills and experienced staff are avalable would be a more effective way of training thand sending further experts to Korea.

The opportunity was offered to the Director of the Research Center to send staff to the toxicology laboratories at Smith, Kline and French Research UK where the following expertise is available.

Dosing by all routes in rodents and dogs,
Collection of body fluids from rodents and dogs,
Clinical chemistry, heamatology and urinalysis,
Ophthalmoscopy, electrocardiography and gastroscopy in rodents and dogs,
Reproductive studies in rats, including methods for examination of soft tissues in teratology and behavioural measurements in young rats.

Embryo Culture in Vitro

Cell culture - Thyrocytes, hepatocytes, myocytes, brain and pituitary cells

Endocrinological studies

Radio Immune assays

Whole body autoradiography

III RESULTS

Staff in the Research Center have shown a great enthusiasm to improve their technical and theoretical knowledge of toxicology. They have been active participants in discussions during lectures and informally. Improvements to study design and methodology have been readily adopted. New Standard Operating Procedures are being prepared or planned as new equipment and new techniques are acquired.

IV CONCLUSIONS

Much has already been achieved by the Research Center but a great deal more remains to be set up. Long term rodent studies using gavage must be developed. Experience with other routes of administration is needed nd collection of body fluids must be improved. Reproductive studies must include soft tissue examinations in teratology. Training in the use of dogs as a non-rodent species is essential. Compliance with GLP to a standard acceptable to International Regulatory Agencies is a prerequisite for the use of the Center as a contract facility by client companies who wish to market their products outside Korea.

longer term perhaps consideration should be given to the development of tissue culture techniques, To achieve these goals and to build upon its present achievements the Research Center should continue its training programme by having further visiting consultants and by sending more selected staff for training aboroad. The completion of the equipping of the facility with basic essentials of apparatus should procede urgently in some areas.

The attitudes of the Director and his senior staff auger well for the future of the Center.