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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

Based on the work of George B. Leslie
expert in general toxicology

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United Nations Industrial Development Organization
Vienna

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EXPLANATORY NOTES

Abbreviations

ECG : ELECTROCARDIOGRAM

KRICT : KOREA RESEARCH INSTITUTE OF CHEMICAL TECHNOLOGY

GLP : GOOD LABORATORY PRACTICE

SOPS : STANDARD OPERATING PROCEDURES

UNDP : UNITED NATIONS DEVELOPMENT PROGRAM

ABSTRACT

This mission forms part of the expert assistance provided for the KRICT Toxicology Research Center in general toxicology as job DP/ROK/82/11-59/32. I.G. It was undertaken between 20th February and 25th March 1988.

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 Regulat ry Agencies.

The staff were given guidance in the form of seminars, informal discussions, written material and samples. Recommendations were made on eqipment and on study design and conduct 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 20th February 1988, during which 21 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 development 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 design, planning, operation and administration of short term and long term animal experiments and specifically to :

1. Evaluate the current status of the facilities, laboratories, equipment, techniques, staff, GLP compliance future needs and priorities.
2. Review the studies in progress and those planned. Assist in the evaluation and interpretation of data and suggest modifications to protocols if necessary
3. Assist in the preparation and translation into English of Standard Operating Procedure .
4. Assist in staff education and training particularly with respect to dog studies.
5. Advise on report preparation and regulatory submissions.
6. Advise the Director on current requirenents and future strategy.

The objectives were achieved by holding many meetings with staff individually and in groups, by holding seminars, by careful review of the various sections and their resources and by detailed discussions on studies and data generated.

RECOMMENDATIONS

The recommendations made after my previous visit are essentially unchanged but three new recommendations are added

1. Compliance with GLP remains a high priority for the Center.
2. The Center must continue to broaden its experience of animal studies and in practicular should now progress into dog studies.
3. The training programme which has been very successfully implemented should continue both in terms of Consultant Experts and in Fellowships for staff to train abroad.
4. A formal system should be implemented to co-ordinate work on a compound between the Department of Toxicology and the Pharmacology Screening Department which is responsible for studies on absorption, distribution, metabolism, excretion and pharmacokinetics. Perhaps a "project manager" should be selected for the organization of work on each new compound. Further training is urgently needed in this area
5. The library facility is inadequate. The Center should subscribe to a number of relevant tournals in Laboratory Animal Science, Toxicology, Pathology and Pharmacology. Standard textbooks in these fields should be available.
6. The Center should begin to collect a background database for all routine parameters.

I. OBJECTS

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

The Research Center has progressed rapidly since its foundation but some areas of general toxicology have yet to be developed. The most outstanding need is to develop the use of dogs for toxicology studies since the use of rodents only is not acceptable to Regulatory Authorites. A dog facility has now been built and it was necessary to advise on the completion of the facility, equipment necessary for dog studies, dog supply, design of studies and technical methodology.

The Center is not yet in compliance with GLP and until this is achieved its studies would not be accepted internationally. Help was therefore given to assist the center to move towards compliance as rapidly as possible.

Long term rodent studies are now being conducted and a main objective was to advise on study design, data collation and interpretation and on the preparation of reports suitable for regulatory purposes.

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. Evaluation of current status

B. Advice on future needs

C. Review of current and planned studies

D. GLP compliance

E. Training

F. Documentation

G. Pharmacology Screening Programme

A. Evaluation of current status.

1. Facilities. In December 1987 the Toxicology Center moved into purpose built new accomodation of 4000 M². In addition to the 8 existing rodent experimental rooms there are now 4 rooms suitable for larger rodents or lagomorphs and 4 experimental rooms for dogs. Associated with these there is a dog quarantine room, a large animal necropsy room and a cage washing room.

The Center has had a substantial increase in office space and has a computer room, an office available for visting scientists and a seminar room.

There is a marked improvement in the provision of laboratory space.

The laboratories available are now as follow :

Experimental Animal Medicine	1
Reproductive Toxicology	2
Pathology/ Rodent Necropsy	3
Genotoxicity	2
Ecotoxicity	2
Environmental toxicity	1
Immunotoxicology	1

Other facilities include :

QAUnit	1
Diet/Drug Mixing Room	1
Drug Formulation Room	1

Most of the experimental animal rooms and laboratories are adequate for their purpose but the dog facility requires some work to be completed before it is operational. The dog room walls and ceiling will have to be covered with sound absorbing material since without this both the dogs and the staff would suffer auditory distress. Staff will have to be given ear muffs when working in this area. The large animal necropsy room will need a ventilated hood in which to operate an electrical bone saw and will need an electro-mechanical disposal unit in the sink drain.

The diet/drug mixing room and drug formulation area require some modifications (see section B)

The immunotoxicology laboratory is not presently in use as such. Very few toxicology facilities undertake immunotoxicology and there is at present no regulatory need to undertake such studies routinely mainly because at present they have little predictive value. I think a higher priority may be to undertake cell culture studies and it might be possible to use this laboratory for that purpose. Sterile laminar flow cabinets would be necessary.

2. Equipment. There has been a dramatic increase in apparatus since my previous visit. A sum in excess of $ 800,000 has been spent on equipping the facility with most of the modern resources which are essential for the statisfactory conduct of toxicology studies. In terms of the choice of equipment the money has been very well spent. A Labcat computer system is now installed, pathology can now undertake a full heamatological profile and a standard range of clinical chemistry and the reproductive toxicology section now has X-Ray facilites.

Genotoxicity, Ecotoxicity and Environmental Toxicity (which are not within my field of expertise) seem very adequately equipped. General Toxicology has about 90 % of the equipment it needs (see section B).

3. Staff. Reporting to Dr. Roh there are now 20 scientists of whom 5 hold PhD's. Eleven of the scientists have veterinary qualifications and the remainder are science graduates. There are 18 technical staff and 1 secretary as well as a computer/WP operater making a total of 41 staff at present. Dr. Han has about 10 potential or actual Study Directors in general toxicology.

4. Techniques And Training. The staff have considerably widened their range of techniques after visits to the Center by consultants and by sending selected staff abroad for training. However these successes still leave many important gaps to be filled in terms of techniques (see section B).

Chronic Toxicity In Rodents (and oncogenicity studies) are now ongoing using dietary administration. Gavage will inevitably be required on a much larger scale than at present and more staff will have to become proficient in this technique as well as in other routes of administration. Improvements must be made to the animal identification system. A tattoo method is ideal but failing that an ear punch system must be adopted. I suggest that Mr. G. Conybeare should initiate this. A more formal method for recording clinical observations during long duration chronic toxicology and oncogenicity studies is also an essential task which can be undertaken by Mr. Conybeare.

Reproductive Toxicology seems to be moving forward very well since Mr. Kim's recent 3 month Fellowship in Japan and techniques should improve further after the visit to the Center by Dr. Kawanishi in May. Segment I and II studies (Teratology) in rats are currently undertaken and Mr. Kim and his colleague Mr. Park are expecting to perform studies for Segment III rat and Segment II rabbit studies in the near future. Skeletons can now be examined by X-Ray or by double staining with

alizarin red and alcian blue. There are some problems being encountered at present with autoclaved diet causing skeletal abnormalities. I have suggested that Mr. Conybeare should be consulted on questions of dietary composition.

Dog Studies have not yet begun but Mr. Sin has recently completed a 3 months study Fellowship in Japan on dog techniques. Mr. Conybeare's current consultancy visit should provide an opportunity to train staff in technical methods for dogs and I have explained some aspects of study design and data interpretation. Dog studies should be feasible during late 1988 if room changes and apparatus are forthcoming.

Genotoxity, Ecotoxicity and Environmental Toxicity are not within my area of expertise but from an outsider's newpoint they seem to have established most of the relevant techniques. I have reviewed the SOP's for genotoxicity and found them very thorough and comprehensive.

Pathology is very well equipped and now has the ability to undertaken most types of clinical pathology assays (but not coagulation parameters see section B) and can process slides. I did not meet Dr. Ha since he is on an overseas trainning Fellowship but in my view it would be very prudent for the next few years to have histopathology reports checked by an outside experienced consultant. Dr. W. Butler is competent to do this but there are many others who might be suitable (Dr. K. Isaacs & Dr. J. Faccini for example - I can send their addresses if required) and for really difficult problems on oncogenesis the wisest course would be to consult Dr. F. J. C. Roe who is one of the world's leading authorities in this field.

Metabolism and Pharmacokinetics are not undertaken in the Toxicology Department but are the responsibility of the Pharmacology Screening Department. Some aspects of this area do not seem to be covered at present (see section B).

B. Future Requirements and Priorities.

1. Facilities. With the occupation of the new building no new experimental animal rooms or laboratories should be required in the next couple of years. Thereafter the requirements will depend on the level of contract work which is forthcoming. Once the Center is in compliance with GLP and can offer a full range of toxicology studies it may be able to obtain contracts from Japaness companies which presently send the bulk of their contract work to Western Europe. The Center has potential advantages in price and proximity

As discussed in Section A some rooms still require completion, modifications or fittings.

I recommend the following :

i. Change the dog quarantine room for the guinea pig room since this has a better floor drainage system.

ii. All dog rooms need sound absorbent material on walls and ceiling to reduce auditory distress to animals and staff (Staff will have to be equipped with ear muffs).

iii. The large animal necropsy room will need a ventilated hood in which to use an electrical reciprocating bone saw for brain removal. One sink in the room will be used for opening the alimentary canal. The drain on this sink will need a heavy duty electrical waste disposal unit. The floor material will have to changed from tiles to a material proof materal. The necropsy room may well be used for other purposes. It would be suitable for techniques which could not be conducted in the experimental rooms e.g. Electrocardiography, Ophthalmoscopy, Minor Surgery, Intravenous Infusions. For this reason I suggest that the room should have wall and ceiling sound absorbent cladding. It may be more flexible to use a moveable necropsy

table rather than a fixed one. The room will also need a flexible hose system for use during exsanguination. Ceiling power points should be installed.

iv. The cage washing room may also be used for bathing dogs. It needs bigger sinks or baths large enough for dog cages, metabolism cages and a high pressure hose.

v. The dog experimental room lobbies will need low benches fitted for use for collection of blood, intravenous injections and other techniques away from the distraction of other animals. A foot rail would be very useful. Cupboards will be needed to hold dosing solution, capsules, tablets, syringes, paperwork etc.

vi. The diet/drug preparation room needs to be divided by an internal partition to separate its two major functions

a. Preparation of dosing solutions, suspensions, capsules etc.

b. Mixing drug with powdered diet .

The latter will cause some dust to be distributed and this could compromise the dosing formulation work by contamination. Dust extraction systems should be installed around mixing machines which should be in dust containment chambers.

vii. Close to the new building there is a small temporary building which was previously used for rabbits and large rodents. This building should be retained for use as a store for dog diet, metabolism cages and infusion tables etc. The alternative would be to use a valuable laboratory or experimental animal room in the new building.

2. Equipment. Most of the present requirements are associated with the need to offer dog studies. The following items will be needed :

* Cages
* Metabolism Cages
* Electrocardiograph
* Slit Lamp large ophthalmoscope
  Tattooing device (hypograph)
  Arterial Blood Pressure Monitor
* Necropsy Table - moveable
  Reciprocating Bone Saw

* Coaguliser (for automatic coagulation parameters)
* Electric Clippers
  Pumps, Tables and jackets (for intravenous infusions)
* Weighing Scales _ up to 30kg
* Necropsy Instruments
  Electronic balances for necropsy
  Blood Mixers
  Anaesthesia Equipment
  Steriliser
  Items marked * are ESSENTIAL

Apart from this equipment for dogs there are only a few items of basic equipment which are missing. I would like to see the reproductive section buy a Double-Headed Binocular Microscope for training staff to examine foetuses and for consultations on abnormalities. The diet preparation area needs a small scale mixer for preparing compound/diet mixes for mice (the one presently used for rats is too big for mice) and consideration might be given to purchasing a pelleting machine. One glaring omission is the lack of facilities to undertake Whole Body Autoradiography of rats. This is essential for distribution studies. Liquid nitrogen facilities and a very large (sledge) freezing microtome are needed. A "hot box" is needed for rodents for blood sampling.

3. Staff. I understand that in April it is hoped to recruit another 5 technical staff. This is essential to free scientific staff from routine animal work. Beyond that the future requirements will depend on the level of contract work to be undertaken and on the decision to develop new areas of expertise (in vitro toxicology, inhalation, immunotoxicity etc.).

   More staff are needed in the pharmacology screening department.

4. Techniques and Training. The UNDP sponsored programme of Visting Consultants and Overseas Training Fellowships for staff have been immensely successful in enabling the Center to reach its present standards. It is to be hoped that this programme will continue since a great deal of training in techniques and report preparation has yet to be done.

Chronic Toxicity in Rodents (and Oncogenicity Studies) have not yet reached the stage of reporting. These studies generate huge quantities of data which have to be reported in a standard succinct form. I have tried to teach Study Directors something of the approach which is required and have left the Center with copies of some guidelines for preparing reports for regulatory purposes. I feel however that some help will be needed in the future when very large long term studies have to be reported. Training will also be needed on the clinical examination and necropsy of geriatric rodents. Mr. Conybeare would be an ideal person to do this and I suggest he should return when the first oncogenicity study reaches its late stages. New paragraph an essential task for the Center from now onwards will be to collect and pool data for all parameters from central animals to build up a databank of current normal ranges of values. This is required to enable study directors to assess the significance of small differences between control and treated group values.

Reproductive Toxicology. No further training would seem necessary in the near future on the standard in vivo "regulatory" studies but I think consideration should be given to training staff in the newer investigative in vitro techniques of Rat Embryo Culture and Limb Bud Culture. A Fellowship could probably arranged for a member of staff to spend some time in the U.K. at Cambridge University, Imperial Chemical Industries, Smith, Kline & French and Life Science Research.

Dog Studies. After the facilities and equipment necessary for dogs have been installed it will probably be necessary to have further training for the staff on techniques such as Electrocardiography, Ophthalmoscopy, Blood Pressure Recording, Urinary Bladder Catheterisation,

Necropsy, Clinical Examinations, use of Vermifuges, Mange Treatment, Gavage, Inter-rectal, Inter-vaginal, Intravenous and Intramuscular routes of administration. Many of these techniques could be demonstrated by Mr. G. Conybeare but the more specialised veterinary skills should be taught by a laboratory animal veterinarian. I would recommend Dr. S. Whitehead who is secretary of the British Laboratory Animals Veterinary Association.

For the interpretation of ECG's it will be necessary to send a member of staff on a Fellowship. The world's leading authority is Dr. D. Detweiler in the University of Pennsylvania Veterinary School in Philadelphia, USA. He is now semi-retired but might be willing to train someone. I would be happy to contact him if required.

It will also be necessary to have someone trained in dog ophthalmoscopy. Dr. K.C. Barnett, Director of the Small Animals Health Trust at Newmarket in the UK would be an ideal teacher in this field if someone is sent to England on a Fellowship. If not Dr. Whitehead could begin to train someone.

Metabolism and Pharmacokinetics. Since these are studied in a separate department from toxicology it is essential that bridges are established to co-ordinate the work of the two departments. Metabolic data and pharmacokinetic studies are essential adjuncts to the design and conduct of toxicology studies. The staff in the pharmacology department who are few in number have responsibility for running various screening programmes as well as for metabolic and pharmacokinetic work. I am not convinced that staff in either department are as yet clear about the types of metabolic, pharmacokinetic and pharmacodynamic studies which are essential to toxicological evaluations. I propose that a consultant should be assigned to one of the

departments for a month and suggest Dr. Richard M. Lee. Dr. Lee is a consultant in drug Absorption, Distribution, Metabolism, Excretion and Pharmacokinetics, with about 30 years experience in the pharmaceutical industry.

It is essential that the Center should develop the technique of whole body autoradiography as soon as possible. Dr. Lee could assist with this.

I think it might help the co-ordination of metabolic and pharmacokinetic work for toxicology studies if for each sponsored research compound one of the Study Director level of staff was appointed to manage the collaborative work on the project.

Other. Consideration should be given to setting up techniques for cell culture in the future. This is an important new field in toxicology and will soon become a feature of contract house work.

C. Review of Current and Planned Studies.

The major contract on which the Center is currently working has reached the following stages :

Acute Toxicity (gavage)	: rat	- Completed
1 month toxicity (diet)	: rat	- Completed
3 months toxicity (diet)	: rat	- Completed
Segment I reproductive	: rat	- Completed
Segment II reproductive	: rat	- Current
Chronic (12 months) toxicity (diet)	: rat	- Current
Oncogenicity (diet)	: rat	- Current

In general these studies are being run very competently and data are being recorded in a satisfactory manner. The study directors will probably need some expert assistance when they are preparing their reports on these studies, particularly in the case of the 12 months and oncogenicity studies. The Center's pathologist will also need assistance in the presentation, interpretation

and reporting of his data. The studies conducted by diet used fixed ratios of drug to diet. It would have been better if the diet drug ratio had been adjusted in line with the variation in food consumption and the increases in body weight.

The pharmacokinetic and metabolic data on which these studies were based was not adequate and for future study designs coordination of this work should be improved. Dog studies on this compound will be essential.

D. GLP Compliance

The Center is not yet in compliance with international GLP requirements. Standard Operating Procedures which are an essectial feature of GLP are now being prepared. Last year I brought over 400 from England but the Center has opted to base its SOP's on a set obtained from Japan. At present most of these are in the process of being translated from Japanese to Korean and cannot therefore be reviewed by someone who can read neither language. The SOP's for genotoxicity studies have reached the stage of being translated into English. I reviewed these and made some amendments to the English grammar and spelling. In general I found them thorough, clear and very detailed. If the other SOP's are of this standard the Center will be well on its way towards compliance once they are in use. The Center must however take note of the fact that Japanese study protocols differ radically from those used and accepted in Western Europe and North America and therefore to ensure full international compliance the SOP's must be checked once they are translated into English. Some additional SOP's will no doubt be required. CV's of staff and organization plans are required.

Some other aspects of compliance cannot at present be assessed by consultants who cannot read Korean.

E. Training

Seminars were presented to the staff of the Center :

1. Review of studies on KD 106
2. The design and conduct of dog studies
3. The role of the contract toxicology house

Posters were presented jointly with G. Conybeare on :

1. The collection of blood from rodents
2. Gavage to rodents
3. Intravenous infusions in dogs

Training sessions were held with Study Directors on various aspects of data collection, interpretation and reporting. A training videotape of various techniques was presented in collaboration with G. Conybeare.

F. Documentation

The Center was provided with :

1. Training videotape.
2. Copy of U.K. Regulatory Guidelines MAL2 + Supplement.
3. Guidelines for Study Directors on report preparation.
4. Guidelines on conduct of GLP audit.
5. U.K GLP Compliance Programme.
6. Copies of material presented in poster form
7. Copies of all teaching materials prepared for seminars were distributed in advance to those attending.
8. Notes on reproductive toxicology protocols.
9. Brochures on animal and diet suppliers and on equipment for dogs etc.

G. Pharmacology Screening Programme

I was asked to make suggestions about the requirements of the screening programme in terms of improving its range of techniques for screening purposes and for conducting pharmacodynamic evaluation of compounds undergoing delelopment. My suggestions were as follow :

A. Cardiovascular profiles in anaesthetised cats.

Cannulation of trachea, femoral artery and vein. Electronic stimulation pre and postganglionically of ascending, acutely decentralised, cervical sympathetic nerve. Record respiration, arterial blood pressure, heart rate and tension in nictitating membrane. Observe direct effects of drugs and modification of responses to noradrenaline, tyramine, acetylcholine, angiotensin II and pre and post ganglionic sympathetic stimulation

Buy

Grass 1 x Polygraph 4 channel pen recorder (model 79)

" 1 x Heart rate meter (model 7944)

" 1 x Force displacement transducer (model FT03)

" 4 x Driver amplifiers (model 7DA)

" 3 x Preamplifier bridge circuits (model 7P1 d.c.)

Statham 1 x Blood pressure transducer (model P023)

Harvard Apparatus 1 x Cat operating table

" 1 x Multispeed infusion pump

" 1 x Ventilation pump

" 1 x Electronic stimulator (model 50-7422)

" 1 x Rectal digital temperate probe

" Cannulae (trachea, blood vessels)

" Electrodes for sympathetic nerves

Consultant D.F. Weetman

B. Central Nervous System Screen

1. Acute toxicity symptoms and Irwin profile ———— General
2. Prevention of oxotremorine induced tremor in mice — Anti-Parkinson
3. Anti convulsant activity - electroshock and pentamethyline tetrazole in mice ———— Anti-Epilepsy
4. Amphetamine antagonism in rats ———— Neuroleptic
5. Hexobarbitone sleeping time in mice ———— CNS depression or metabolic inhibition
6. Reduction in minimum anaesthetic dose ———— CNS depression of hexobarbitone in mice
7. Reserpine reversal in rabbits ———— CNS stimulation and anti-depressant
8. Open field test in rats ———— Anxiolytic
9. Y-maze in rats ———— Anxiolytic
10. Analgesia-phenylbenzoquinone writhing in mice ——— Weak analgesic
11. Analgesia-hot plate, electroshock of pressure in inflammed foot ———— Strong analgesic
12. Electroshock induced aggression ———— Anxiolytic & neuroleptic

Consultant D.F. Weetman

C. Ligand Binding

Isolated receptor membranes from rat brains are incubated with a tritiated specific receptor ligand. After equilibration, incubate with test compound then measure the displaced radiolabelled ligand. This technique measures the specific receptor affinity of test compound. Consult : Dr. J. M. Sneddon

D. Guinea Pig Ileum (and other *in* vitro isolated organs)

Effect on responses to acetylcholine, nicotine, histamine, barium, electrical stimulation, etc. Plus direct effects. Consultant D.F. Weetman

On my return to the U.K I will contact Dr. Weetman to ask him to send further details of some these techniques.

III. RESULTS

The staff of the Research Center have improved their understanding of study design, data collection, data collation and data interpretation. They are progressing towards GLP compliance and are inproving their range of technical competence and experience.

IV. CONCLUSIONS

The Toxicology Research Center has made remarkable progress but still has more to do before it can be said to have achived its objectives.

Full GLP compliance must be its highest priority. Without this the studies being undertaken by the Center on behalf of its clients will not be acceptable for regulatory purposes in other countries.

Dog studies should be initiated as soon as possible and some additional equipment will be needed for these. Dog studies are essential before a drug can be given to man. Studies in rodents should be extended to other routes of administration. More consideration must be given to the organization of drug disposition, kinetics and metabolism studies which are necessary for the design of toxicology studies. This is an area which needs urgent attention.

In the longer term embryo culture and cell culture facilities and expertise should be developed.

A marketing organization will become necessary once the Center can undertake a full range of studies to international standards since its future development will depend on the value of its contracts. Perhaps Consideration should be given to establishing links with one of the major multinational contract companies.

In order to achieve these objectives it will be necessary to continue the training of the staff by the use of visiting consultant experts and by further training of staff on overseas Fellowships.

The continuing enthusiasm and the developing expertise of the staff should ensure the successful progress of the Center

V. ADDENDUM 1

** Equipment required **

Dogs	Dog cages
	Dog metabolism cages
	Electrocardiography
	Slit lamp ophthalmoscope
	Hypograph
	Aterial blood pressure monitor
	Necropsy table
	Reciprocating bone saw
	Coaguliser - automatic coagulation parameters
	Electric hair clippers
	Infusion pumps - Harvard Apparatus
	Infusion table - Harvard Apparatus
	Weighing scales for dogs - mechanical
	Blood mixers
	Anaesthesia equipment
	Steriliser
	Electronic balances for dog necropsy
	Dog jackets - Harvard Apparatus
Others	Double headed binocular microscope -reprotox.
	Small diet/drug mixer
	Pelleting machine - Buhler Miag
	Heavy sledge freezing microtome for WBAR
	Liquid nitrogen facilities for WBAR
	Rodent hotbox - Harvard Apparatus

V. ADDENDUM 2

** Possible Consultants **

Consultant	Purpose	When
G. Conybeare	Dog studies Oncogenicity necropsies	At end of rat oncogenicity study Jan/Feb 1989 ?
K. Isaacs	Pathology data collation Interpretation and presentation in report	Mid 1989
R.M. Lee 73 Arlesey Road Ickleford. Hitchin U.K	Absorption, distributio, metabolism, excretion, pharmacokinetics, autoradiography	1988 - URGENT NEED
J.M. Sneddon The William Harvey Research Institute ST. Bartholemew's Hospital Medical School Charter House Square London ECIM 6BQ U.K	Ligard binding (pharmacology screening department)	1988
D.F. Weetman	Cat cardiovascular profiles CNS screening In vitro isolated organ techniques (pharmacology screening department)	1988 - When cat qequipment is installed - Sept ?
S.M. Whitehead The Squirrels Old Warden Beds U.K	Dog techniques, ECG's ophthalmoscopy animal supply, breeding and husbandry.	1988 When dog studies are commended

V. ADDENDUM 3

** Possible Overseas Training Fellowships **

1. In vitro rat embryo culture & limb bud culture

   Cambridge University + Industry in U.K

2. Electrocardiography

   Dr. D. Detweiler, University of Pennsylvania, Philadelphia, USA

3. Dog ophthalmoscopy

   Dr. K.C. Barnett, Newmarket, U.K

4. Mammalian (including human) cell culture techniques

   Various industrial laboratories in U.K