COFOPEX Ltd.

Toxicological studies and Research and Development with Radioactive Materials

COFOPEX LTD.
Bimbó út 92.
1022 BUDAPEST
HUNGARY

- Our laboratories regularly work for partners from overseas, among our customers are: the USA, Canada, Japan, China, Brazil, India, Malaysia, Russia and South Africa.
- Our laboratories has international accredited title, our studies are GLP qualified.
- At concrete request according to work we give an individual calculated price within 2 days which is in every case lower and more favourable than the international price level.
- We provide an immediate start of the work to all our clients, on condition that the material which should be studied, the necessary complete documents arrive to us as well as the 100% of the price of the study.
- The needed documents and plans for the completing of the studies as well as the reports will be written in English.
- Contact of our company:

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tel/fax: 36-1-336-1800

Who We Are

A world-class non-clinical contract research organization located near Budapest, Hungary. The facility excels in client service and is highly regarded for its responsiveness. We are also proud of our quality services and scientific expertise.

With over 35 years of experience, the facility provides an extensive list of services to agrochemical, chemical and pharmaceutical markets. We have complies with Good Laboratory Practice (GLP) and studies are conducted in accordance with the regulatory requirements of the OECD, ICH, FDA, EMEA and OPPTS.

The facility includes 54 animal rooms with rigorously controlled environmental conditions and also 2,500 square metres of state-of-the-art laboratories.

Why Choose Us?

- The scientific staff averaging approximately 20 years of experience
- State-of-the-art facility with strict electronic monitoring of environmental conditions
- Excellent quality controll and assurance
- Competitive cost-quality rate

OUR PHILOSOPHY

We are well aware of the most important factors of success therefore we guarantee all our customers professional services meeting the two criterias of

EXPERTISE AND TIMELESS.

General toxicology

General toxicology tests are the basic set of tests conducted using animals such as rodents, rabbits, guinea pigs, mini pigs, dogs and non-human primates in order to assess the potential toxicity of chemicals in humans.

We offer a wide array of in vivo studies performed in modern facilities with advanced equipments. The objective is to provide reliable and accurate data for further assessment relating to human and environmental exposure.

Main study options

single dose

short or long-term repeat-dose

continuous administration tests

dose-range finders

carcinogenicity

neurobehavioral

in utero exposure

local irritation tests

Species

mice,

rats,

rabbits,

guinea pigs,

mini-pigs,

canine

Administration routes

oral (gavage, dietary, capsule)

dermal, intradermal

intranasal

intravaginal

intravenous,

subcutenous,

intramuscular,

intraperitoneal,

intratracheal

inhalation

Observations/measurements

clinical observations,

food and water consumption,

body weight,

ECG,

blood pressure,

body temperature,

clinical pathology,

necropsy,

organ weight,

histopathology etc.

Reproductive and developmental toxicity

Reproductive and developmental toxicology deals with the identification of the effects of pharmaceuticals and chemicals on the mammalian reproduction at all stages of the developmental process.

We have performed reproductive toxicity studies for pharmaceuticals, agricultural and industrial chemicals in accordance with the OECD, ICH, FDA, EMEA and OPPTS guidelines.

Main study options

- Fertility and reproduction studies (one, two generation studies, combined repeat dose toxicity with repro screening test)
- Prenatal developmental toxicity studies (assessment of skeleton and soft tissues)
- Perinatal and postnatal studies (neurodevelopmental, immuno-developmental studies)
- Combined general toxicity-reproductive toxicity studies

Genotoxicity

Genetic toxicology studies are conducted to evaluate the mutagenic and carcinogenic potential of consumer products, drugs and agricultural chemicals on DNA or chromosomes focusing on the process of mutagenesis including DNA damage, gene mutatations and chromosome aberrations.

Main study options

Bacterial reverse mutation assay (AMES)

Mammalian gene mutation test (mouse lymphoma assay, HPRT, in vitro)

Chromosome aberration test (in vivo)

Micronucleous test (in vitro)

DNA repair test (unscheduled DNA synthesis, in vivo, in vitro)

TK testing in mouse lymphoma cells

Ecotoxicology

We conduct a wide range of ecotoxicology studies in aquatic and terrestrial systems for agrochemical registration and industrial chemical notification. Since each chemical has different physico-chemical properties and the administration route is complex in case of aquatic toxicology tests, the analysis of the test medium is essential in ecotoxicology tests.

Both the tests and the analytical support is performed in accordance with OECD, EPA and Japanese guidelines.

Main study options

Acute fish, algae, daphnia, lemna

Daphnia reproduction

Fish early life-stage

Honey bee acute oral/contact

Earthworm acute/reproduction

Analytical chemistry

The analytical department is equipped with state-of-the-art instrumentation (HPLC, LC/MS, LC/MS/MS etc) to be able to offer a wide range of product characterization studies necessary for registration purposes.

Main study options

Method development/validation

Dose formulation

Characterization of test substances

Stability determination of test substances

Analysis of biological samples

Quality Assurance Unit (QAU)

GLP includes a set of regulations governing the operation, personnel qualification, facility requirements involved in the process of toxicological assessment of drugs and chemicals.
Our QAU unit assures the compliance with these regulations during the test procedures.

QAU responsibilities

Inspection of all study-related documents (study protocols, reports etc.)

Inspection of raw data

Inspection of study procedures

Inspection of personnel qualifications/training

Review of Standard Operating Procedures (SOPs)

Reach Services

We are is familiar with the requirements of REACH and we offer a full range of services to all chemical companies:

• Toxicological testing

• Determination of physico-chemical properties

• Ecotoxicological testing

• Read-across, QSAR modelling

• Risk and exposure assessment

• Preparation of Chemical Safety Reports

• Compilation of the "complete" registration dossier and submission to ECHA via IUCLID 5 or REACH-IT.

Research and Development with Radioactive Materials

Educated stuff of the enterprice consist radiopharmacists, veterinarians, physicist, chemist, bio-engineer and nuclear medicine technicians, animal keepers with many years experience. Their activities are wide-scaling – basicly regarding to medicinal and veterinary isotope applications. Theire work involves preparing the governmental rules, writing the laboratory methodology of the topic, researching actual problems and the contimous postgradual education of the specialists in the field. Registered, licensed isotope laboratories for in vitro work, isotope animal house have been available equipped with dose calibrators, gamma-, beta- racks, whole body and SPECT camera, ultrasonography, x-ray, access to nano SPECT/CT, CT and MRI.

In the Nuclear Medicine Departments of hungarian hospitals a couple of scintigraphical examinations is a daily routine as well. For performing these diagnostical procedures, most importantly needed the detecting instrument (gamma camera) and the brunch of diagnostical radiopharmaceuticals. There is a few dozens of radiopharmaceuticals for diagnostical purposes, most of them are ^{99m}Technetium labelled molecules e.g.: ^{99m}Tc MDP for bone scintigraphy, or ^{99m}Tc MIBI for heart perfision studies – but also in Hungary there is an increasing number of positron emission tomography (PET) examinations that is performed by the use of positron emitting radiopharmaceuticals e.g.: (^{18}FDG and ^{14}C-methyonin). Similarly to the international trends the use of radiopharmaceuticals in treatment protocols is also increasing in Hungary. Nuclear medicine treatment methods are mainly used in cancerous patients but there are many orthopaedic and other diseases also treated by therapeutical radiopharmaceuticals. The best known and frequently used therapeutical radiopharmaceuticals are ^{153}Samariummal and ^{177}Lutecium labelled phophonates (^{153}Sm and ^{177}Lu EDTMP) for bone metastases palliation, ^{131}J-iodine for thyroid diseases, and ^{90}Yttrium-colloids for radiosynovectomy in therapy resistant chronis arthritis patients.

Radiopharmaceutical application must be effective (sensitive and specific in the diagnosis and effective in the treatment) and paralelly fullfill all the requirements of safety. Applied radiopharmaceutical opens numerous chapters of public health : it must be harmless for the patients and their family, for the examining stuff (nuclear medicine technicians and physicians) and for the environment. The use of radiopharmaceuticals is operated by many governmental and european laws and rules that are contimously renewed, rewritten, and constructed for the ever changing practice and educated, communicated with the clinician specialists. These duties are addressed for the Department`s and Experimental Animal House workers.

- Radiopharmaceuticals given into the patient by different routes (intravenam, per os, subcutaneously, intratumorally, intraarticularly) distribute within the organism, concentrate in the target organs, while the extraproportion of applied radiopharmaceuticals leave the body via the urine, faeces and other excrets e.g.: saliva. The timing of distribution and excretion processes together with physical properties of the isotope (physical half-life, type and energy of radiation) determine the *internal dosimetry* data of the patient. Ideally, high target doses exist with low

excretory or critical organ doses. Reaching this goal of clinicians radiopharmaceutical research and development on experimental animals is needed. Animal test`s data are extrapolated in humans using special softvers (MIRDOSE, OLINDA). Our experimental work on laboratory animals goals to minimize the radiation side effects and maximize effectivity of nuclear medicine diagnostical and therapeutical achivements in the human subjects.

- There are many ways in modifying patient internal dosimetry data so that higher target organ dose and lower critical organ doses could be reached. Telling the same in other words finding the *maximum tolerable dose* of a radiopharmaceutical is maybe the most important criteria of radiopharmaceutical application. Using animal models methods could be offered for blocking the thyroid glands, and decreasing the organ doses of the kidneys, liver, gastric mucosa and intestines or the bone marrow.
- There are only very limited data on examined or treated human patients regarding to the excreted proportion of radiopharmaceutical in milk of breast-feeding women and sperm. What time can women start to breast-feed their children? How long should men avoid from sexual interaction? Answering these questions animal test data are necessary for sure.
- An ever rising problem when human or veterinary diagnostical or therapeutical nuclear medicine applications are performed – do we need hospitalization or can we do it ambulatory. What are the criteria of rejecting human and veterinary patients, what we should offer and what to restrict for them? These basic questions should be handled by us at the level of governmental laws and prescriptions and the level of patient and owner information brochures as well.
- Work with open isotope sources while radiopharmacists, nuclear medicinists and technicians do radiopharmaceutical production, preparation, distribution and at Nuclear Medicine Departments in hospitals preparation of syringes, applicating the dose, imaging – the whole process must be safe and harmless for the specialists doing their job. Fullfilling this goal staff continously must be educated, steps of nuclear manipulations must be exercised with animal tests mimicing the clinical situations. A good example the sentinel lymph node detection in human oncological patients where all steps of isotope labelled agent preparation, application of radiopharmaceutical, scintiimaging (scanning), intraoperative detection as well as the pathological examinations of the nodes could be well evaluated and exercised by animal modelling. Experiences of animal tests could be provided for human and veterinary nuclear medicine specialists as local offers.
- Isotope wastes roduced by human or nuclear medicine applications are potencially dangerous for the environment and the earth population that is why handling of them needs special knowledge. These kind of wastes are never only pure isotope wastes but they are also mixed with biologically (excrets), physically (sharp blades, needles), chemically (medicines, solvents). Handling, minimalizing, short term storage and neutralizing of these dangerous wasted materials is an interdisciplinar special challenge for the specialists working in the field.

In vitro activities

- radiolabelling of different carrier molecules with gamma-, beta-, positron and alpha emitting nuclids.
- ITLC and radioHPLC for QC of labelled materials
- stability studies of labelled ligands incubated in phys salina, buffers and different biological mediums (eg.: blood sera, synovial fluid, urine …) at different temperatures
- in vitro (tumor) cell binding assays
- micronucleus assay, chromosome aberration studies in human, mice, and canine lymphocites

Laboratory animals
Mice (including immune suppressed Nude mice), rats and rabbits in different strains furthermore Beagles are available for normal biodistribution studies and diagnostic imaging studies. The same scale of animals are also available for pathological models.
Spontaneously occurring animal diseases

A large number of referred oncological, endocrinological, orthopaedic … dog and cat patients have been presented for diagnosis and treatment. Most often effectivity studies could be carried-out in them.

Appendix

Figure 1a

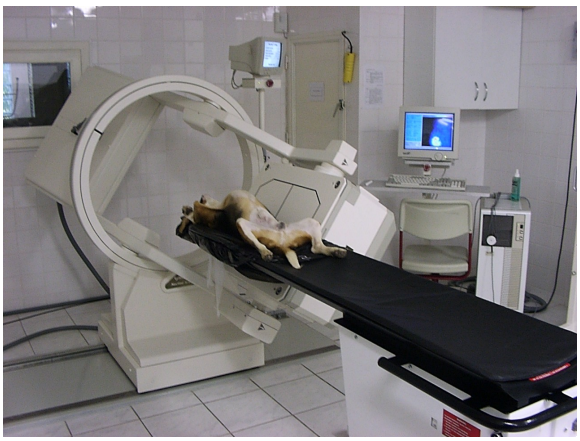


Figure 1b

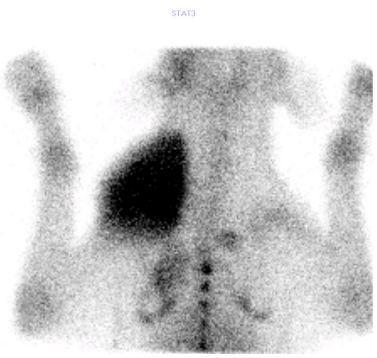
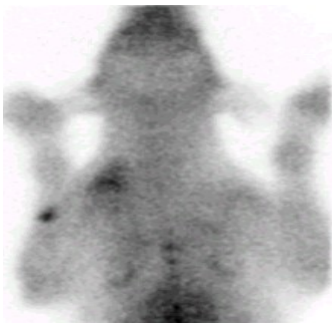


Figure 1c

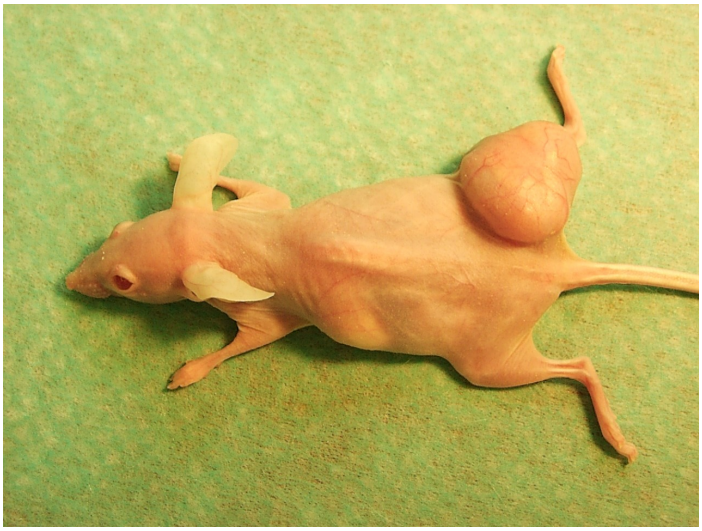


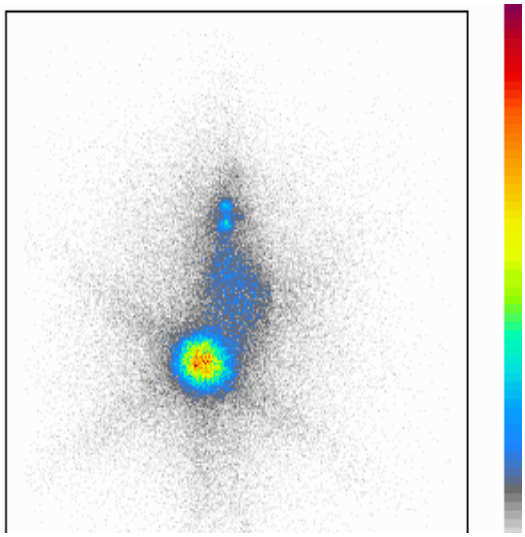
In the photo there is an anaesthetized dog seen during scintigraphic examination (Fig 1a). By performing oncological scintigraphy efficacy of the therapy in malignant diseses could be well

followed-up. In the Fig 1b one can see a huge inoperable tumor before treatment, and in Fig 1c the posttreatment small-sized, operable malignancy is seen.

Figure 2a

Figure 2b





In Fig 2a there is a immunosuppressed so-called Nude mouse is seen, in the right thigh region a transplanted human gastrointestinal cancer is growing. This modell is very much available for testing the availabness, effectivity and harmless of radiopharmaceuticals. In Fig 2b a scintigraphic image of the same mouse is presented, the suspected efficacy of the radiopharmaceutical (^{131}J-anti CEA MoAb) in human malignant diseases is well-demonstrated in the scan.

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