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GLP Certificate holder

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PRECLINICAL RESEARCH AND DEVELOPMENT

vaccines, ophthalmic diseases, osteoarthritis, inflammatory diseases, oncology

COMPREHENSIVE PRECLINICAL SAFETY PROGRAM

human & veterinary drugs, biological, medical devices, food/feed additives, chemicals

DISEASE MODELS

chronic glaucoma, influenza, osteoarthritis, diabetes, contact dermatitis

ACCREDITED BREEDING FACILITY

Beagle dogs, non-human primates

MediTox s.r.o.
Czech Republic
e-mail: surova@meditox.eu
www.meditox.eu

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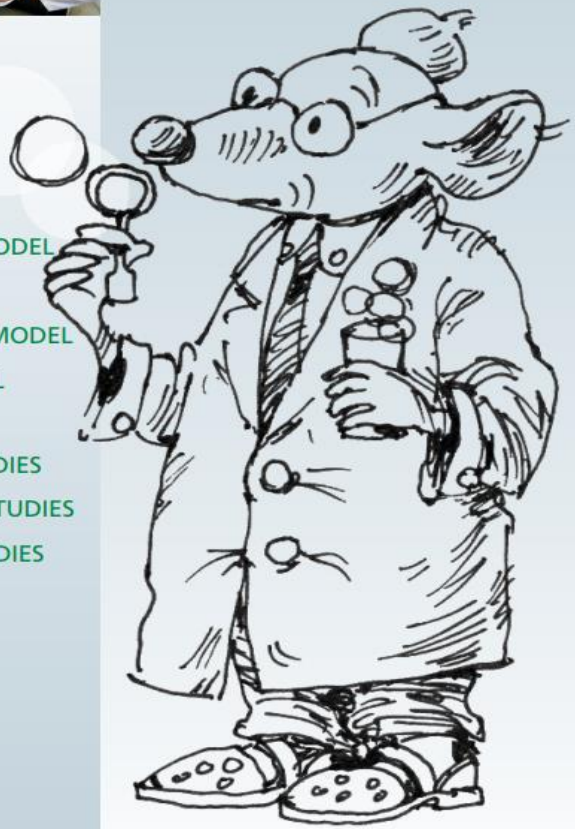
CHRONIC GLAUCOMA
OSTEOARTHRITIS MODEL
COLORECTAL CARCINOMA MODEL
CHRONIC COLITIS MODEL
NON-ALCOHOLIC STEATOSIS MODEL
CONTACT DERMATITIS MODEL

TARGET ANIMAL SAFETY STUDIES
DENTAL HYGIENE EFFICACY STUDIES
IMMERSION / WASH OUT STUDIES



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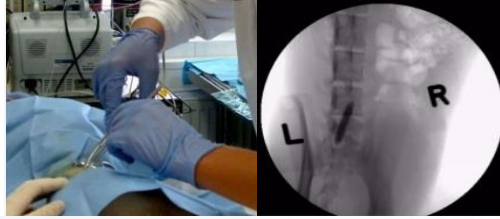
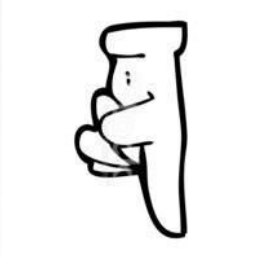


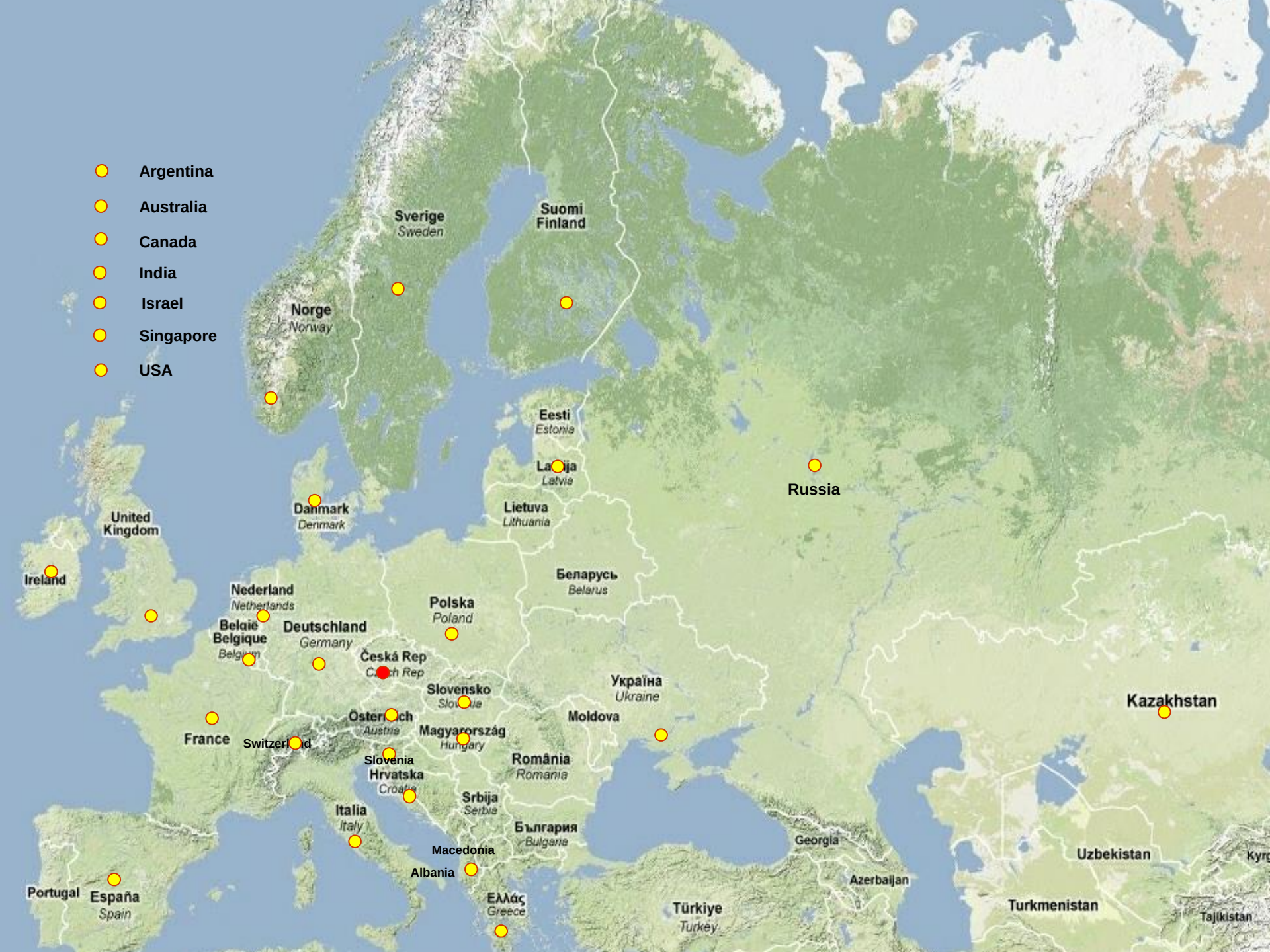
Do you know what is the main goal of preclinical toxicology?

No, it is not to prove your drug candidate/product is safe

A major objective of preclinical toxicology is to provide appropriate information for a compound to proceed safely through clinical trials to registration.



…You are inventing; we are able to move your thoughts in the right direction.
Let´s work together…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Lietuva
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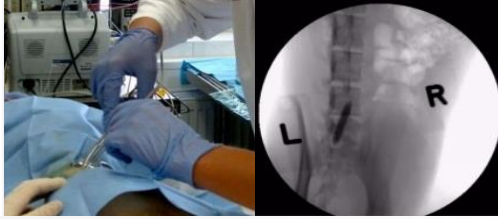


Main actvities

Preclinical R&D

Preclinical development in area of vaccines, ophthalmic diseases, osteoarthrosis, diabetes, inflammation bowl disease

Comprehensive toxicology/safety program

Human & veterinary drugs, biological, medical devices, food/feed additives, chemicals & agrochemicals

Disease models

Chronic glaucoma, osteoarthrosis, influenza, wound healing, diabetes type II,

Laboratory animal breeding

Non-human primates, dogs

Certification

Good Laboratory Practice Certificate OECD GLP [C(97)186 Final] Pharmaceuticals, medical devices and food additives (PHARMA)

Good Laboratory Practice Certificate OECD GLP [C(97)186 Final] Chemicals, agrochemicals (REACH)

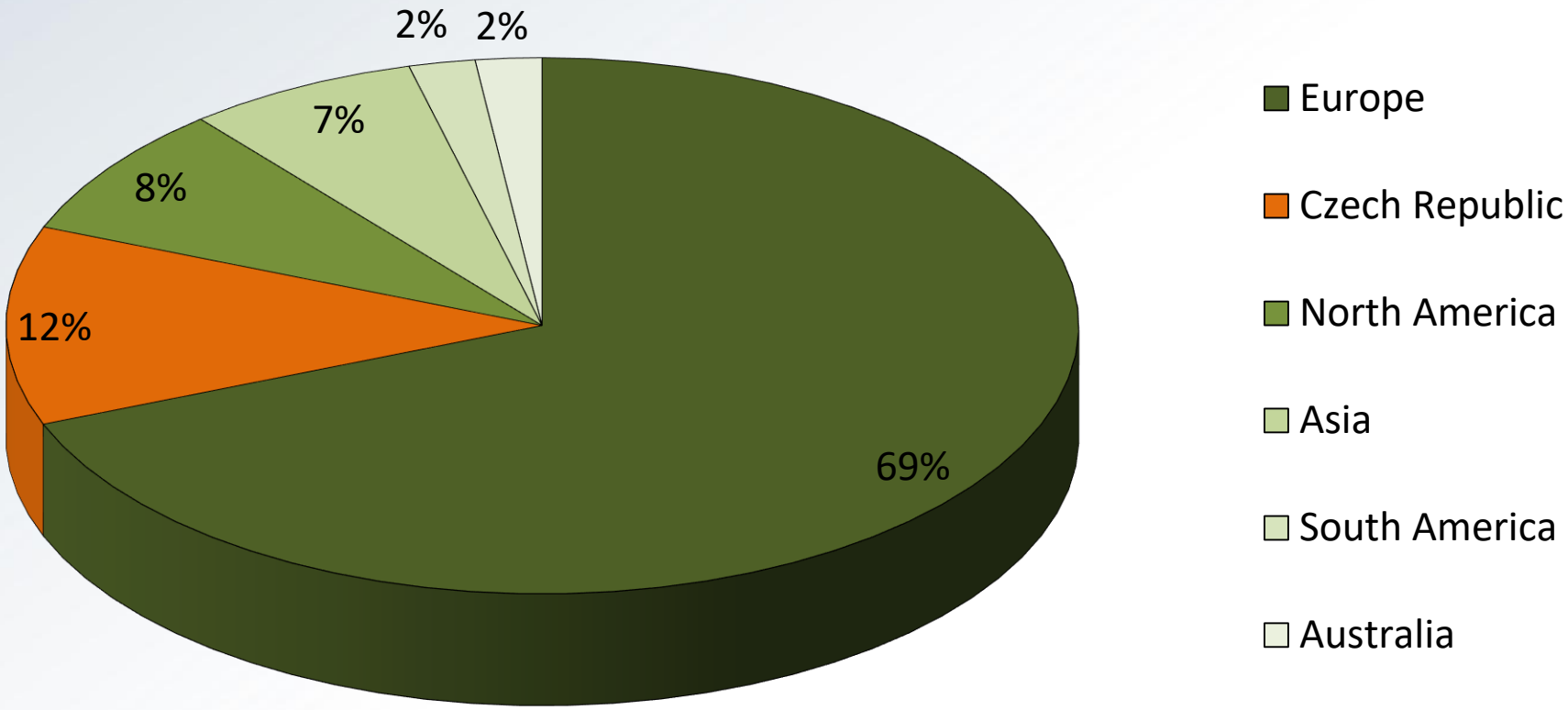
Authorization for Using of Experimental Animals
The Central Committee for Animal Protection of the Ministry of Agriculture

Authorization for Breeding of Experimental Animals
The Central Committee for Animal Protection of the Ministry of Agriculture

Approval for handling with GMO in compliance with Act No. 153/2000 Coll.

Summary information

Structure of clients



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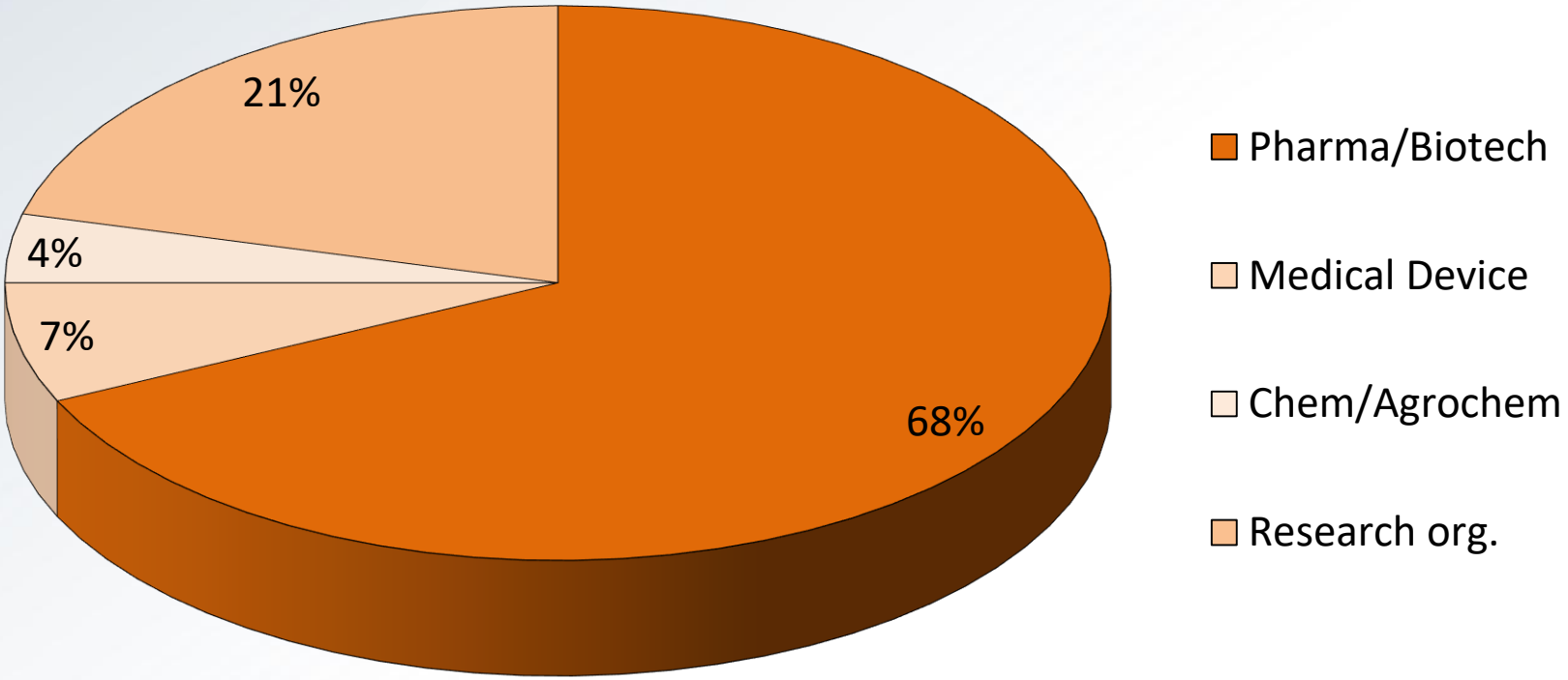
Summary information

Structure of clients



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Selected R&D projects

FLUVAC

Live attenuated replication-defective influenza vaccine

Austria (AGBT), Germany, Russia, Slovenia, Czech Republic

ANTIFLU

Innovative anti-influenza drugs exluding viral escape

Denmark, France, Germany (MPI), Hungary, Israel, United Kingdom, Czech Republic

OSTEOGROW

Novel morphogenetic protein-6 biocompatible carrier device

Austria, Bosnia and Herzegovina, Croatia (UZ), Czech Republic, Sweden

MOTIF

Microbicide optimization through innovative formulation for vaginal and rectal delivery

Czech Republic, France, Italy, United Kingdom (KCL)

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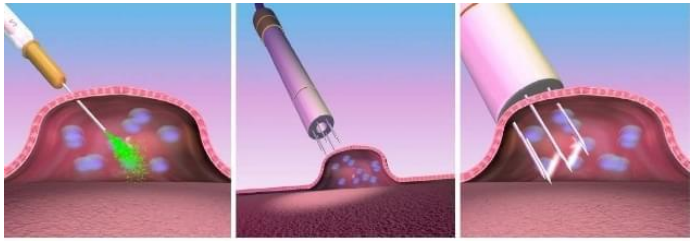
New R&D project

Project of IMI - Call 21: **Development of therapeutics and diagnostics combatting coronavirus infections**

The project aims at developing novel and effective gene-based vaccines that activate the immune response against 2019-nCoV by means of innovative genetic strategies based on gene engineering and a multi-purpose and efficient device based on the mechanism of in vivo electroporation mediated gene transfer (EGT).

MediTox s.r.o. shall cover non-clinical part (studies in rats, dog and NHP) of the project using advantage of

- broad skills in non-clinical toxicology
- and EGT technology already implemented



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Species available	
Non-rodent	Non-human primates, dogs, rabbits, ferrets, cats, pigs, mini pigs
Rodent	Mice, rats, hamsters, guinea pigs
In vitro	Bacteria (*S. tph, E. Coli*), mammalian cells (human lyphocytesm erythrocytes, murine fibroblasts, etc.)
Administration routes available	Buccal, cutaneous, intra-articular, intra-cardial, intra-dermal, intra-muscular, intra-nasal, intra-peritoneal, intra-vitreal, intra-venous, ocular, oral, rectal, subcutaneous, vaginal
	Implantation (bone, muscle, subcutis)

Genetic toxicology	
Gene mutation in bacteria (Ames test)	*S. tph., E. coli,* OECD, ICH,
Mammalian chromosome aberration test *in vitro*	Human lymphocytes OECD, ICH
Mammalian erythrocyte micronucleus test *in vitro*	Human erythrocytes OECD, ICH
Cytotoxicity test *in vitro*	Murine fybroblasts ISO 10993
Test under prepration	
In vitro mammalian cell gene mutation test (MLA) (proposed put in operation: January 2021)	OECD, ICH

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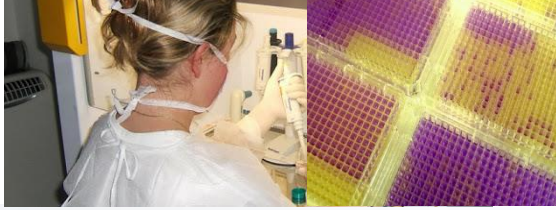
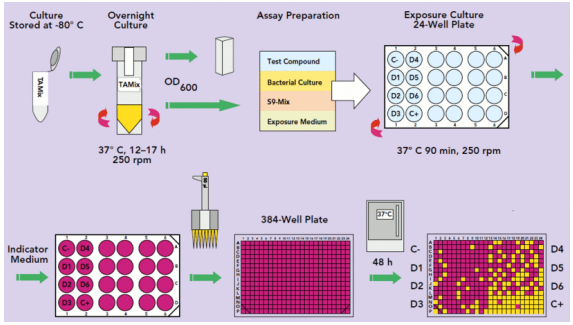


Newly implemented tests/studies

Mutagenicity in bacteria – micro-fluctuation method:

… based on the same principle as the Ames test but uses a liquid, low-volume microplate version of the fluctuation method.

Advantage
- low compound requirement
- increased throughput as compared to the standard format
- processing several replicates at once
- easy colorimetric readout
- less S9 use and less production of hazardous waste due to the low-volume multiwell format.



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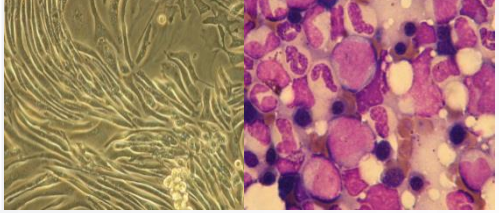


Test under development

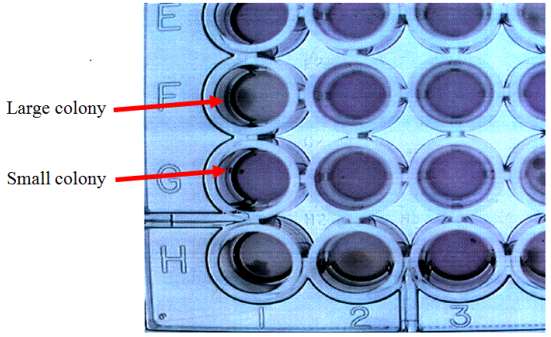
In vitro mammalian cel gene mutation test (MLA)

The MLA test belongs to the basic battery of genotoxic tests and in some countries is explicitly required by regulatory authorities.

Mutagenic effect is based on change of impossibility of cells to synthetize thymidinkinase - mutant cells are able to proliferate in the presence of TFT, whereas normal cells, which contain the TK enzyme, are not.

Advantage: Detection of point mutations and chromosomal aberrations (deletions, mitotic recombination, aneuploidy) in cell culture of mouse lymphoma cells 178Y/Tk+/- in one test

Full implementation expected: 2021



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General toxicology	
Maximum tolerated dose (single dose)	Rodents, non-rodents 3 – 5 dose levels
Dose range finding study (7 – 90 days)	Rodents, non-rodents 3 – 5 dose levels
Pilot, Proof-of-concept studies	Rodents, non-rodents
Single dose (acute) toxicity	Rodents, OECD
Extended single dose toxicity study	Rodents CPMP/ICH/286/95, ICH M3R2
Repeated dose toxicity study (1 week – 6 months)	Rodents, OECD, ICH
Repeated dose toxicity study (1 week – 12 months)	Non-rodents, OECD ICH

Safety pharmacology	
Safety Pharmacology: CNS, CVS	ICH S7
Pharmacokinetics/Toxicokinetics/BEQ/BA	
TK/PK/BA/BEQ studies, rodents, non-rodents (in-life phase)	ICH, VICH, OECD
Non-clinical safety	
Non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals	ICH
Preclinical safety evaluation of biotechnology-derived products, rodents, non-rodents	ICH
Preclinical pharmacological and toxicological testing of vaccines, rodents, non-rodents	ICH
Nonclinical evaluation for anticancer pharmaceuticals, rodents, non-rodents	ICH

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Medical device biocompatibility	
Tests for genotoxicity, carcinogenicity and reproductive toxicity	ISO 10993-3, OECD 471, 473, 475, 474, 487, 490
Tests for *in vitro* cytotoxicity	ISO 10993-5
Tests for local effects after implantation, rodents, non-rodents	ISO 10993-6
Tests for irritation and skin sensitization	ISO10993-10, OECD 404, 405, 406, 429, 431, 438
Tests for systemic toxicity, rodents, non-rodents	ISO 0993-11, OECD 407, 408, 420, 423

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Veterinary drug and feed assessment	
Target animal safety studies	VICH, EFSA
Oral hygiene and anti-plaque efficacy study in dogs	VOHC
Immersion/wash out study of spot-on veterinary products in dogs	VICH
Feed safety studies	VICH, EFSA
Palatability study, rodents, non-rodents	EFSA

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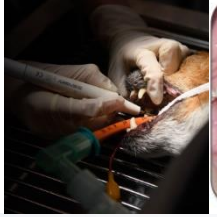


Newly implemented tests/studies

Oral hygiene and anti-plaque efficacy study in dogs (by VOHC)

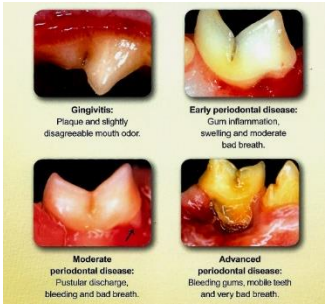
The key to management of gum disease (for humans or pets!) is prevention. As long as the surfaces of the teeth are cleaned frequently, the gums will stay healthy. Excellent oral health is maintained by daily oral hygiene. Exept of daily brushing, daily chewing activities can also be effective in maintaining oral health.

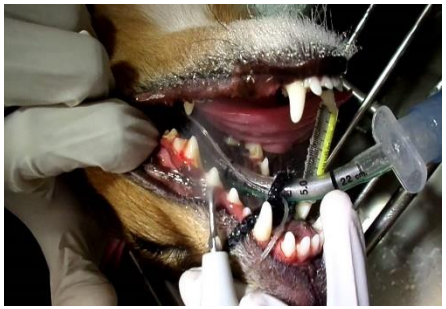
Test procedure:

Day 0 - scaling and polishing the teeth – plaque and calculus scores are zero, gingivitis scoring

Day 1 – x - providing the product tested, daily assessment of general health state

Day x - gingivitis, calculus and plaque scoring by trained scorer according to scoring system by Hennet et al. (Res Vet Sci. 2006; 80: 175-80)





Newly implemented tests/studies

The immersion/washout study of spot on veterinary products

The study documents the impact of dogs with spot-on products on the aquatic environment, especially its remains in surface waters bathing of treated dogs

Advantage - standardized immersion bathtubs covered with innert plastic material

- standardized water temperature allowing standard condition for spon-on product washing into the water

- standardized water sampling protocol

- GLP-compliant study

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Disease models	
Chronic glaucoma (chemically induced)	Dog
Acute contact dermatitis	Pigs
Human influenza	Ferret
Osteoarthrosis (CLT)	Dog
Models under development	
AOM/DSS induced colorectal cancer	Mouse
Chronic glaucoma (chymotrypsin, laser)	Rabbit
Knee osteoarthritis (ACLT)	Rabbit
Non-alcoholic steatohepatitis (NASH)	Mouse

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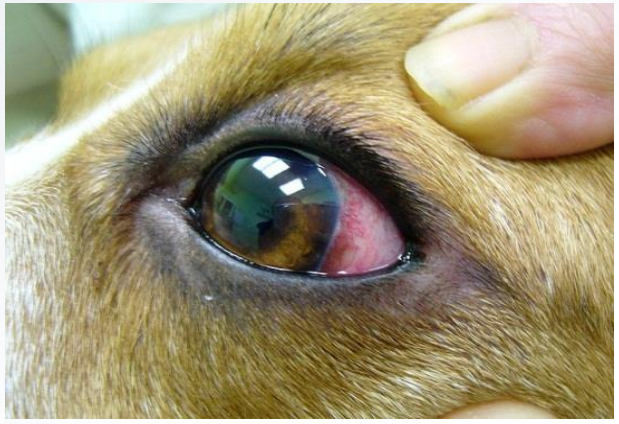
Experimental chronic glaucoma, dogs

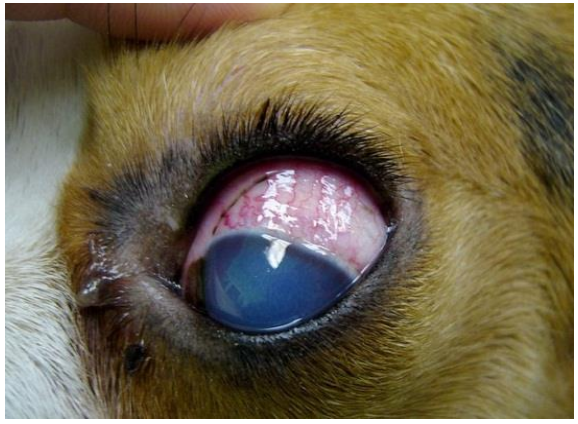
„More than 70 million people worldwide suffer from glaucoma. Glaukoma is leading cause of blindness.“

Induced by intraocular injection of chymotripsine

Revealing chracteristical clinical signs

- **elevation of IOP**
- **corneal opacity**
- **dilated episcleral blood vessels at the corneal edge**
- **reduced or absent pupillary reflex**
- **uveitis.**





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Ferret model for safety and efficacy of influenza therapy

Ferrets (*Mustela putoria*) emulate numerous clinical features associated with human disease; this is especially the case with regard to influenza

Clinical and clinical laboratory features shared by humans and ferret model following virus infection

- Fever
- Nasal secretion
- Coughing
- Serum abnormalitires
- Weight loss and/or anorexia
- Lethargy
- Lymphopenia
- Transmission to susceptible contacts
- Hypercytokinemia
- Distribution of sialic acid in respiratory tract

Models under development

AOM/DSS induced colorectal cancer (mice)

AOM/DSS model is well established approach to study colonic cancer development in short time period, however the tumor progression and overall survival need to be established in given doses of AOM and DSS in ideal time schedule.

Animal model: B6 mice - recently the most commonly used strain with good average sensitivity to the method (develop enough tumors with high overall survival)

Animal sex: male - more predictive, less risk of false positive results (females are less sensitive to CRC development)

Full implementation expected: 2021

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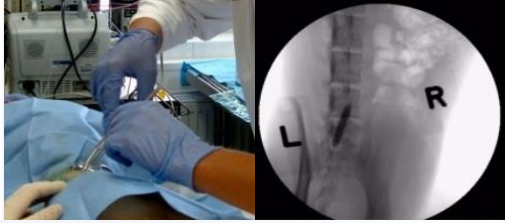

Models under development

Knee osteoarthitis (rabbit)

The prevention and treatment of knee osteoarthritis (OA) is increasingly important in the context of the aging population, both in terms of health-related quality of life and financial burden of disease. Animal models provide practical and clinically relevant ways to study both the natural history and response to treatment.

The rabbit anterior cruciate ligament transection (ACLT) model is increasingly being used in early OA studies.

Animal model: albino rabbit (no single „gold standard“ exists)

Advantage: - easy to use
- rapid and severe changes in articular cartilage and subchondral bone
- knee biomechanics cartilage capable of regeneration

Full implementation expected: 2021

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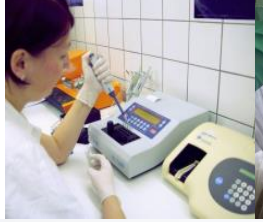

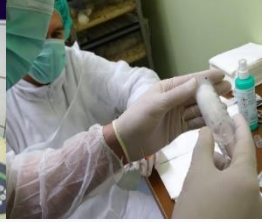

Models under development

Non-alcoholic steatohepatitis, NASH (mice)

Among the emerging chronic liver diseases, non-alcoholic fatty liver disease (NAFLD) and its more advanced form, non-alcoholic steatohepatitis (NASH), are becoming a major health problem. In the Western world, prevalence is estimated to be around 20 to 30% of the adult population, as the disease is associated with obesity and diabetes.

The ideal animal model to accurately simulate NASH is not yet available

Animal model: transgenic strains of mice having genetically engineered liver enzymatic activity.

Dietary model: methionine and choline, HF diet, cholesterol and choline diet etc.

Main task: to select the as best transgenic strain and dietary model as possible

Full implementation expected: 2021/2022

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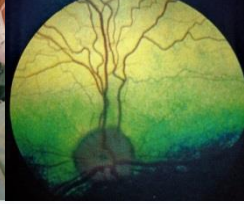

Experimental facilities available

Besides of common conventional and SPF experimental facility for studies in rodents and dogs:

- reconstructed experimental facility for studies in NHP
- experimental facility for studies in cats
- BSL II experimental facility for studies in rodents, rabbits and ferrets
- Experimental facility for studies in mini pigs
- Fully equipped surgical room for conducting studies requiring surgery

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References

Alzprotect, France

Amega Biotech, Argentina

BIOVET AD, Belgium

California Univ, USA

Celon Pharma, Poland

CONTIPRO a.s., CR

DECHRA, USA/UK

DelSiTech Ltd., Finland

EMS, Brazil

Evestra, Germany

Faraday, Inc., USA

FATRO, Italy

GATT Technologies, The Netherlands

Immuneed, Sweden

INEB, Portugal

Klifovet, Germany

KRKA, Slovenia

Lesaffre, France

Mabion, Poland

Nicox, France/Italy

NovoNordisk, Denmark

Olainfarm, Latvia

Orexo, Sweden

Oxford University, UK

Rottapharm, Italy

Sanofi Group (Zentiva)

Sunpharma, India

Univ Hospital Basel, Switzerland

University of Zagreb, Croatia

Triveritas, USA/UK

Vetcare Oy, Finland

Virbac, France

General service flow chart

Event	Responsibility	Approximate duration
1.RFQ	Sponsor	**N/A**
2.Proposal/Quotation	CRO	**3 – 7 days**
3.PQ assessment	Sponsor	**2 – 4 weeks, preferably as soon as possible**
4.If PQ agreed by Sponsor, preparation of Contract	CRO	**1 – 2 weeks**
5.Contract comments	Sponsor	**2 – 4 weeks, preferably as soon as possible**
5.1 TIDS available to CRO	Sponsor	**1 – 2 weeks, preferably as soon as possible after PQ/Contract approval**
5.2 TIDS comments by CRO	CRO	**3 - 7 days**
5.3 Preparation and internal approval of Application for Ethical Approval (EA)	CRO	**3 – 5 daysafter TIDS is completed**
6. Application for Ethical Approval assessment	State Authority (Ministry of Health)	**6 – 8 weeks (up to 40 working days from the submission + 1 - 2 weeks for administration)**
6.1 Preparation of SP and discussion with Sponsor	CRO/Sponsor	**2 – 4 weeks (study pa prepared within EA approval period)**
6.2 Request for test system	CRO	**Rodents: 2 – 6 weeks** **Non-rodents 1 - 6 months (depending on species) before planned study start, usually just after Contract is approved**
6.3 Test item delivery to the Test facility	Sponsor	**1 - 2 weeks before planned start of the study at the latest**
7. Performing of the study	CRO	**As soon as possible after getting Ethical Approval, duration depends on study type**
8. Audited Draft Report submission	CRO	**Within 3 - 10 weeks after the end of in-life phase of the study (depending on study type)**
8.1. Sponsor comments and discussion	Sponsor/CRO	**2 – 6 weeks, preferably as soon as possible**
9. Submission of Final Report	CRO	**1 – 2 weeks after Sponsor approved the Draft Report**

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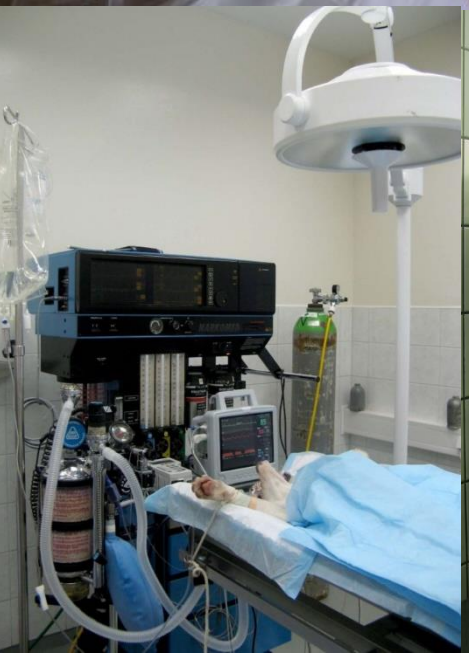

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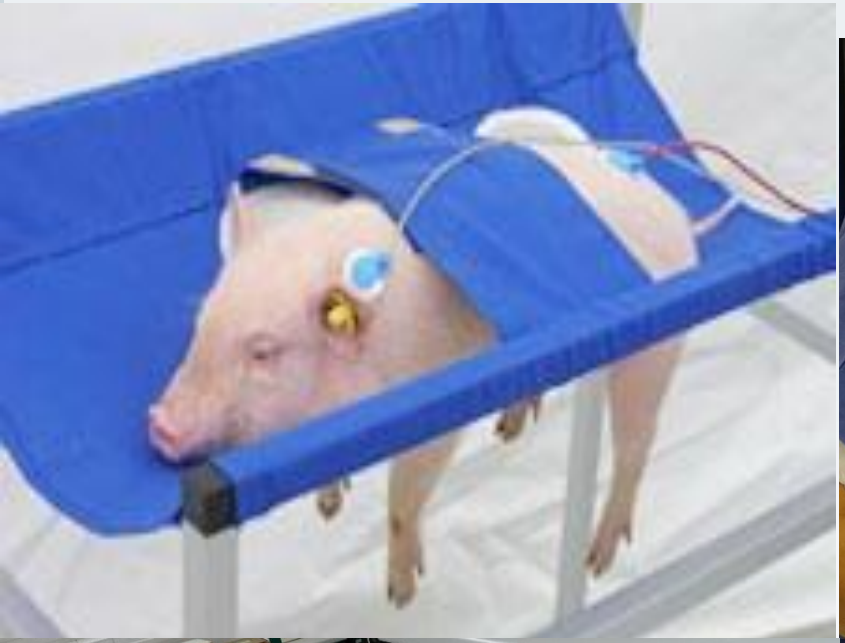

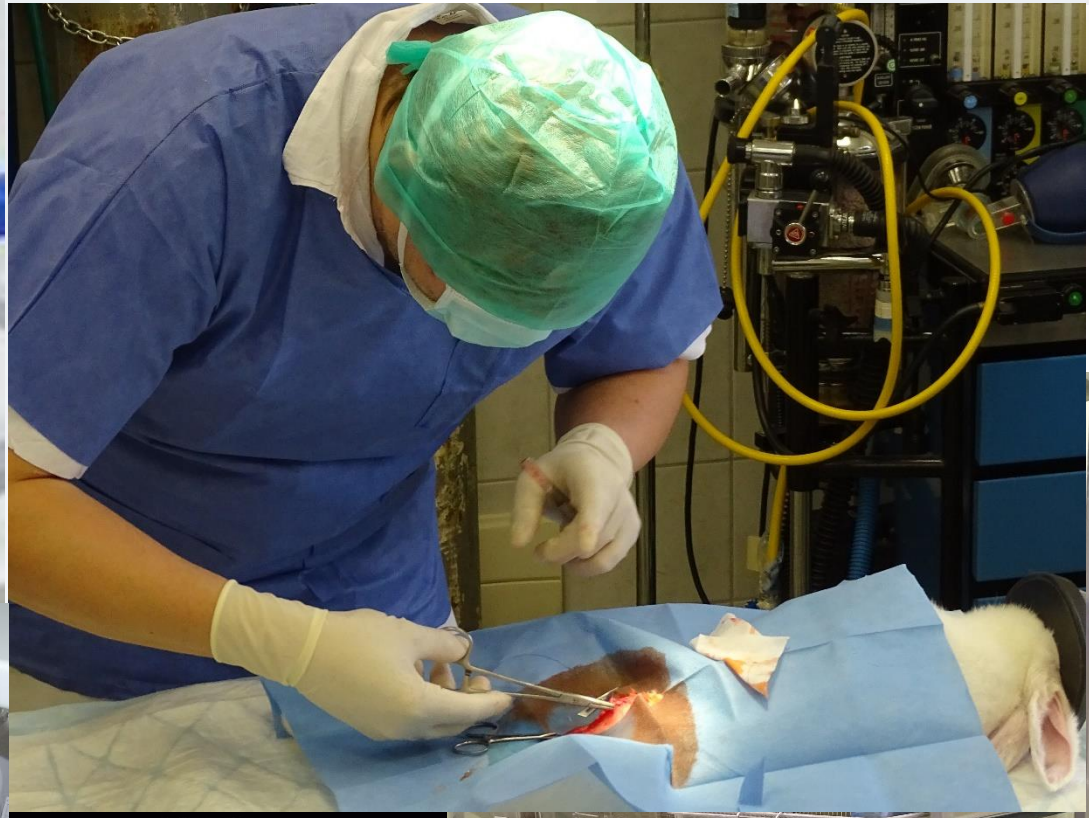

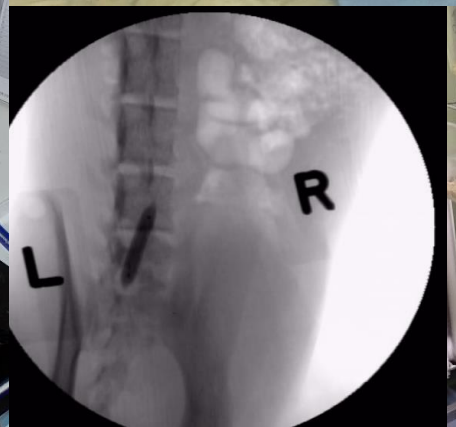

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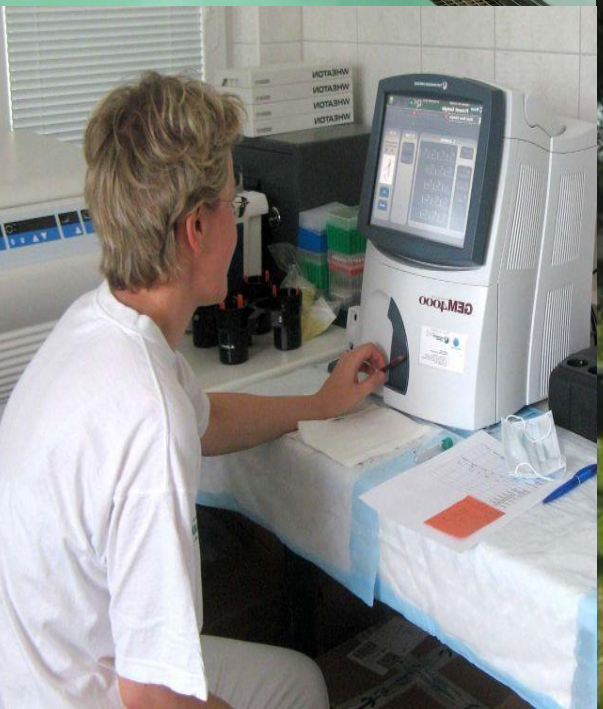

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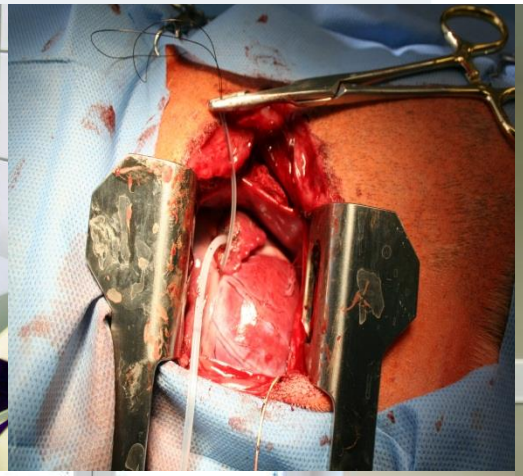

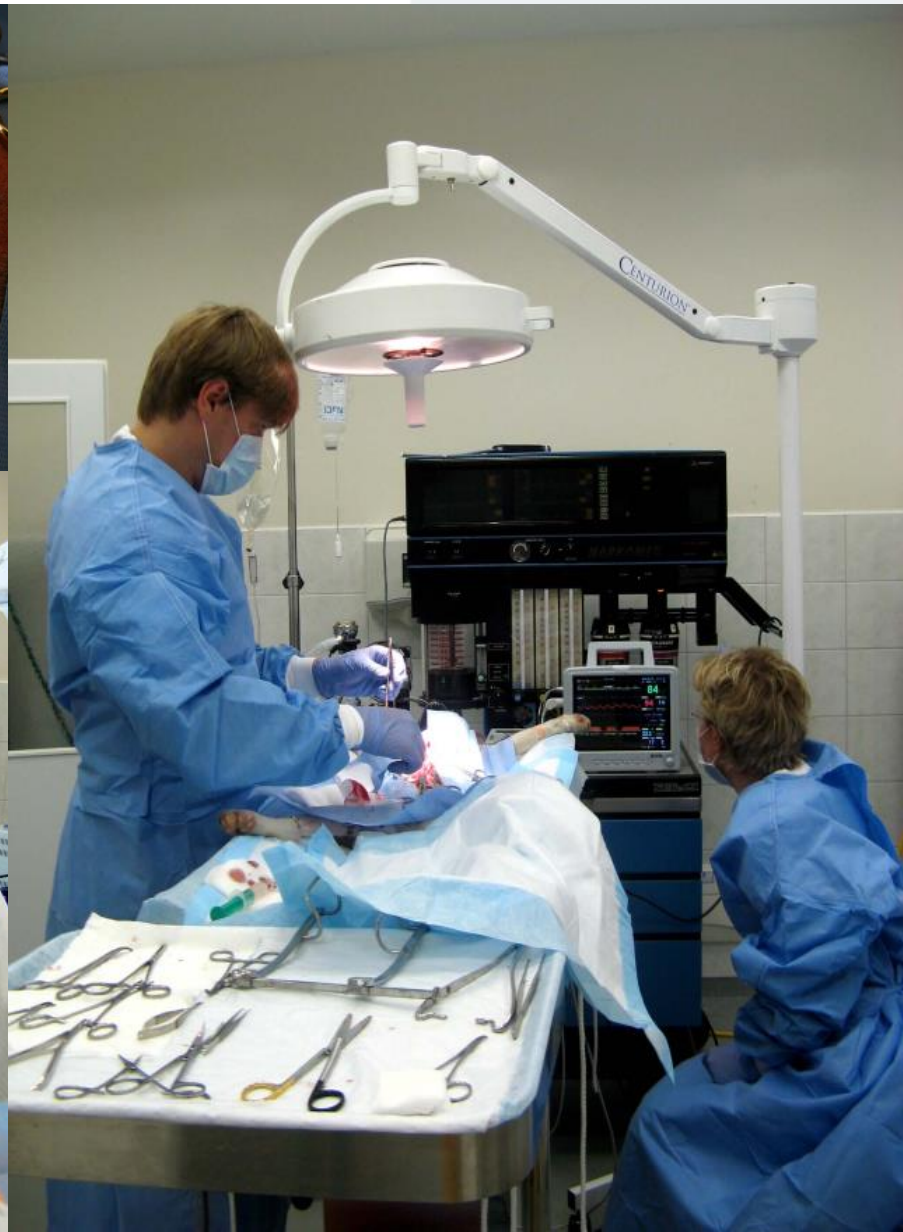

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