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GLP Certificate holder

# MEDITOX

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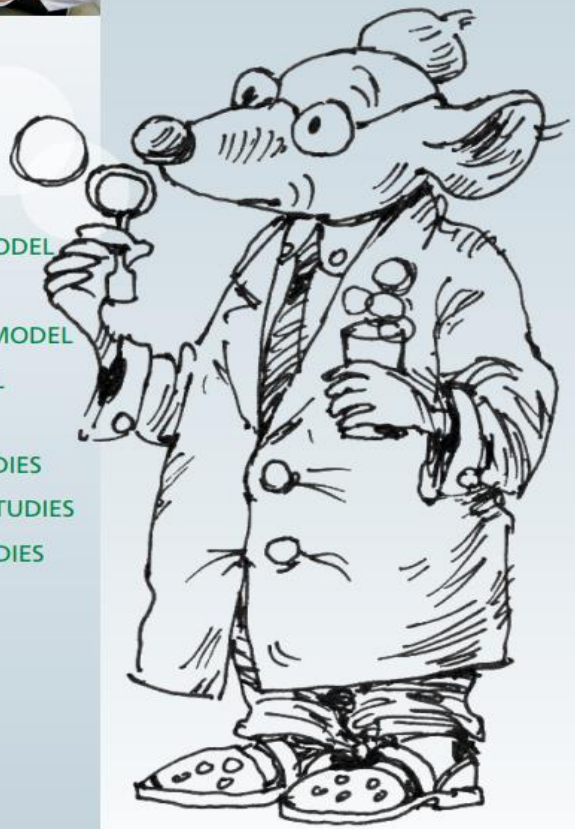
CHRONIC GLAUCOMA
OSTEOARTHRITIS MODEL
COLORECTAL CARCINOMA MODEL
CHRONIC COLITIS MODEL
NON-ALCOHOLIC STEATOSIS MODEL
CONTACT DERMATITIS MODEL

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



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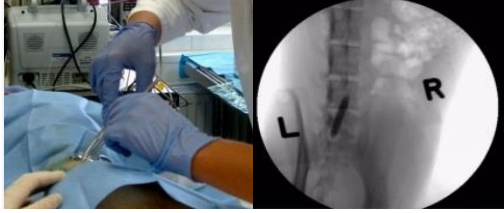
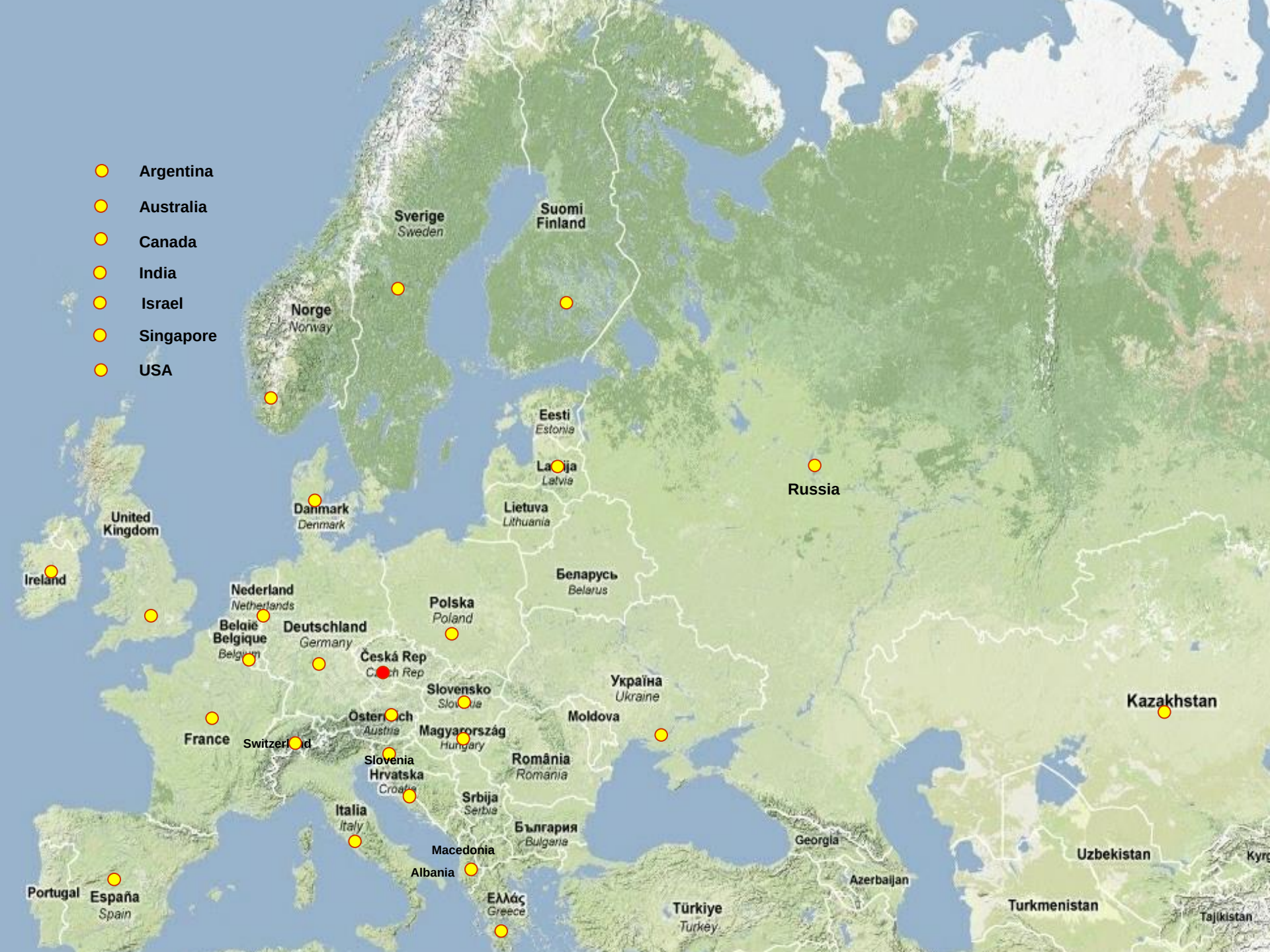



## Do you know what is the main goal of preclinical toxicology?

**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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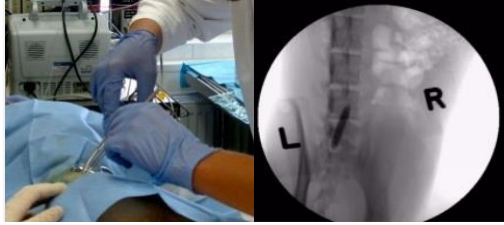



## Main actvities

### 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**

### Laboratory animal breeding

**Non-human primates, dogs**

# Certification

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

**Authorization for Using of Experimental Animals**
The Central Committee for Animal Protection of the Ministry of Agriculture
Valid for 2020 - 2025

**Authorization for Breeding of Experimental Animals**
The Central Committee for Animal Protection of the Ministry of Agriculture
Valid for 2020 - 2025

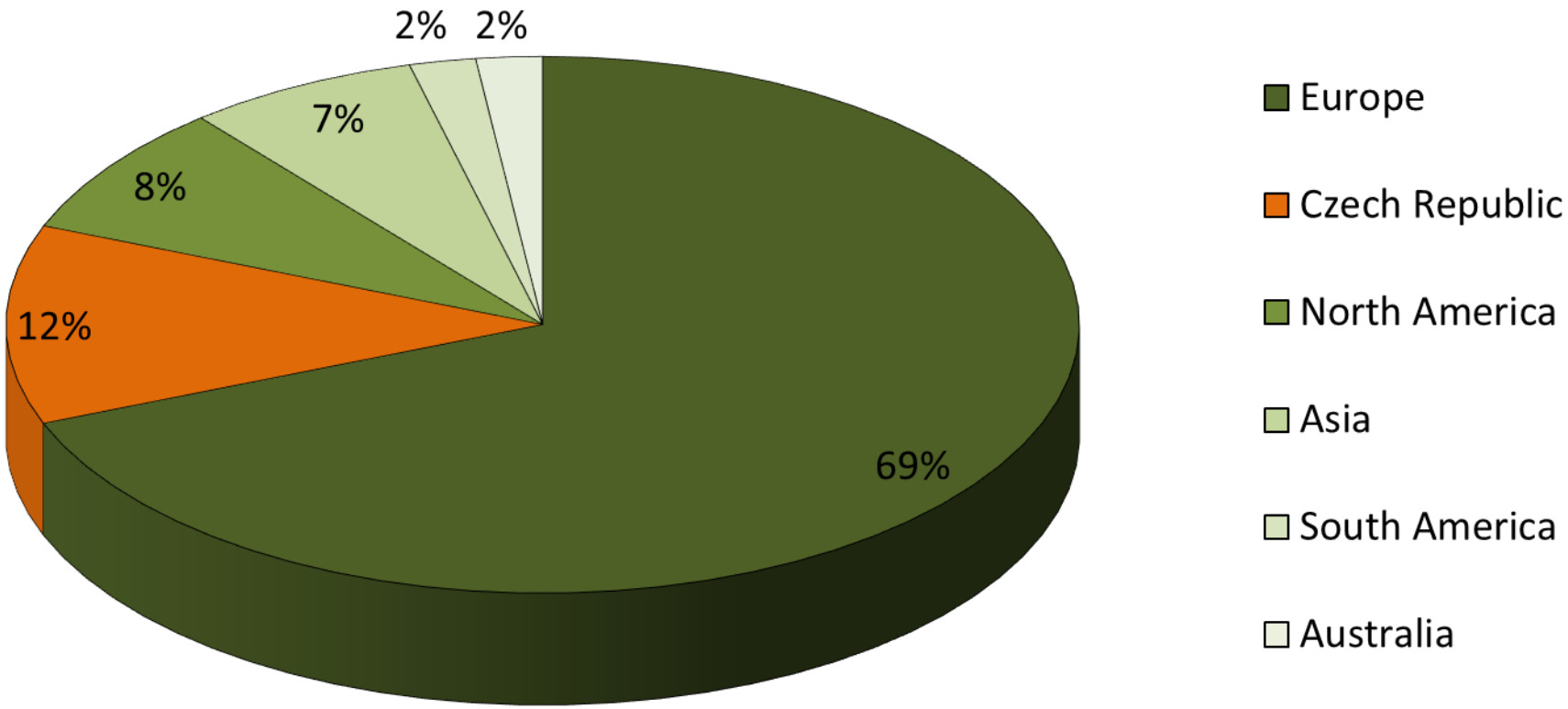
**Approval for handling with GMO** in compliance with Act No. 153/2000 Coll.

**National Institute of Health, Office of Laboratory Animal Welfare (USA)**
Valid for 2020 - 2025

**Crédit Impôt Recherche (CIR) accreditation**
Valid for 2021 - 2023

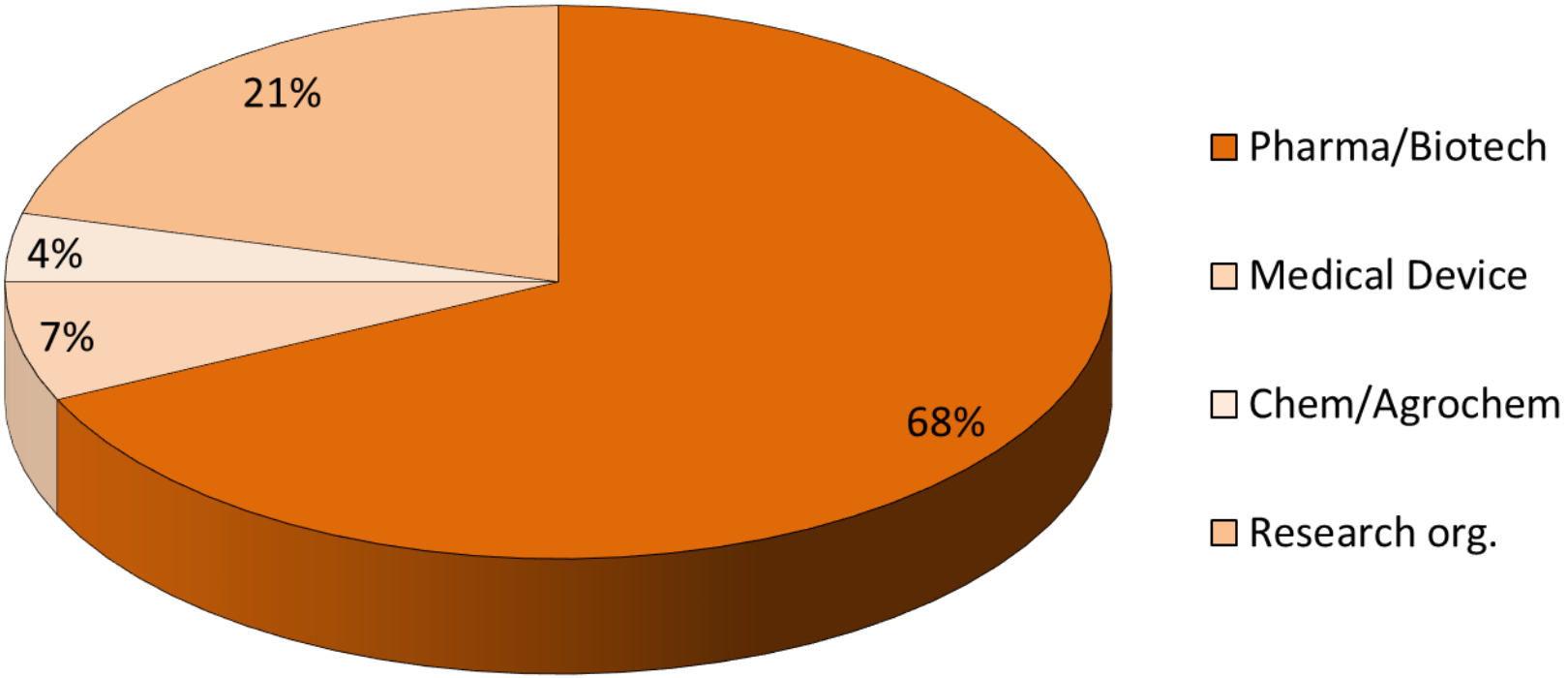
# Summary information

## Structure of clients



# 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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| Test systems available | |
|---|---|
| Non-rodents | Non-human primates, dogs, rabbits, ferrets, cats, pigs, mini pigs |
| Rodents | Mice, rats, hamsters, guinea pigs |
| Cells | Bacteria (*S. tph, E. Coli*), mammalian cells (human lyphocytes, 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, sub-cutaneous, vaginal |
| | Implantation (bone, muscle, subcutis) |

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# Studies/tests available

| Genetic toxicology | |
|---|---|
| Gene mutation in bacteria (Ames test) | *S. tph., E. coli,*<br>OECD, ICH, |
| Mammalian chromosome aberration test *in vitro* | Human lymphocytes<br>OECD, ICH |
| Mammalian erythrocyte micronucleus test *in vitro* | Human erythrocytes<br>OECD, ICH |
| Cytotoxicity test *in vitro* | Murine fybroblasts<br>ISO 10993 |
| **Test under development** | murine lymphoma cells<br>178Y/Tk+/- OECD, ICH |
| *In vitro* mammalian cell gene mutation test (MLA)<br>(expected to run the GLP-compliant test: 2021) | |

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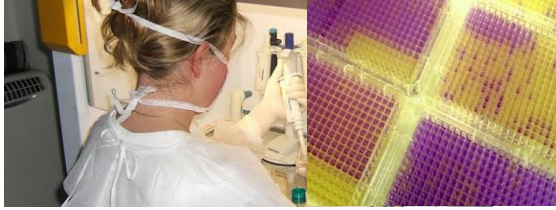
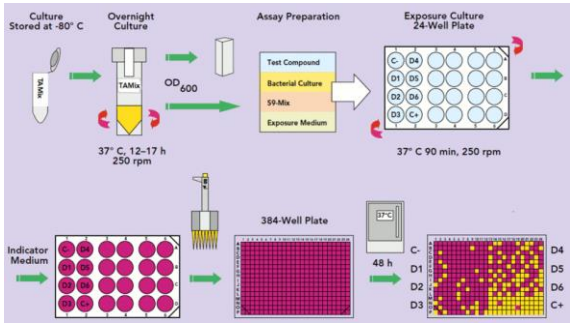


# Newly implemented

## 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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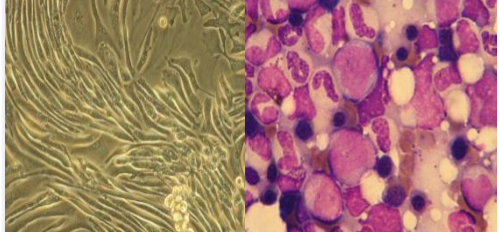


# Test under development

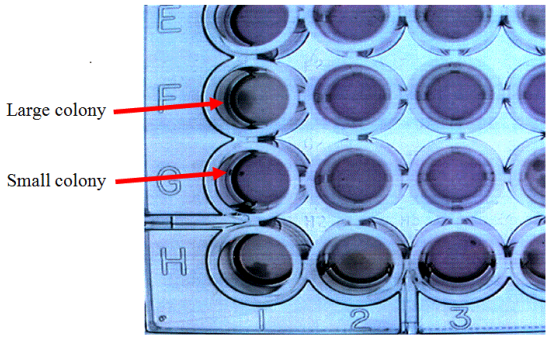
## In vitro mammalian cel gene mutation test (MLA)

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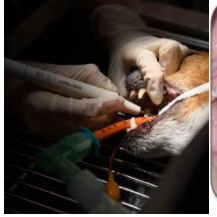



# Newly implemented

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

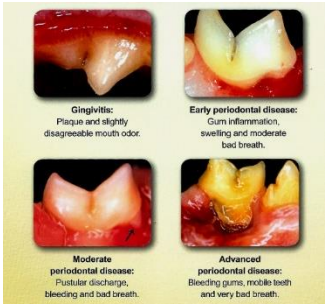
The key to management of gum disease (for humans or pets!) is prevention. As long as the surfaces of the teeth are cleaned frequently, the gums will stay healthy. Excellent oral health is maintained by daily oral hygiene. Exept of daily brushing, daily chewing activities can also be effective in maintaining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

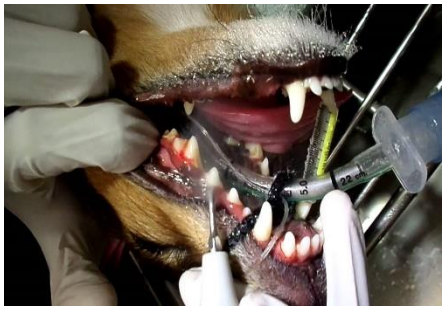
**Test procedure:**

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)



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# Newly implemented

## 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 | |
|---|---|
| Chronic glaucoma (chymotrypsin, laser) | Rabbit |
| Knee osteoarthritis (ACLT) | Rabbit |
| | |

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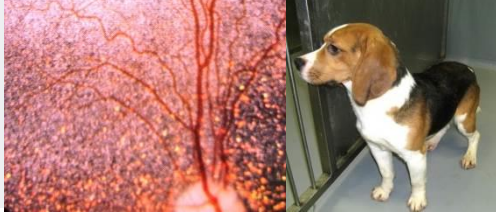


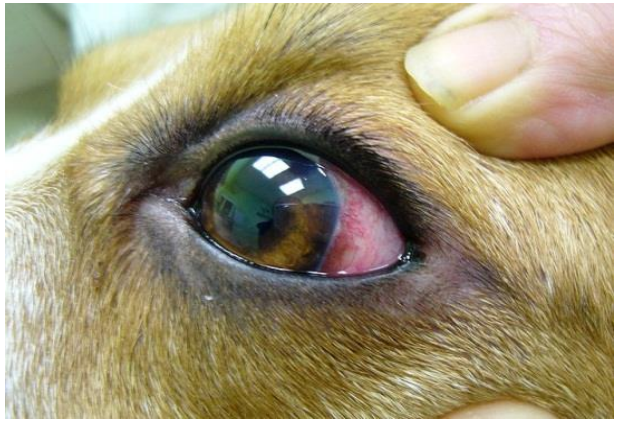
# Experimental chronic glaucoma, dogs

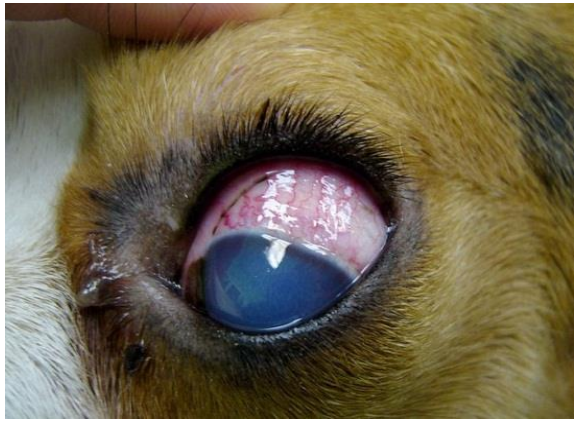
***„More than 70 million people worldwide suffer from glaucoma. Glaukoma is leading cause of blindness.“***

**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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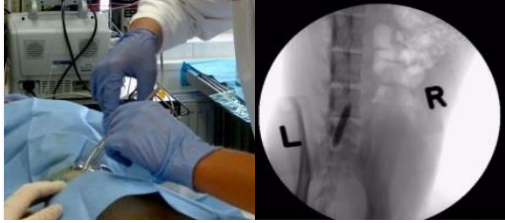
# Ferret model for safety and efficacy of influenza therapy

**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

**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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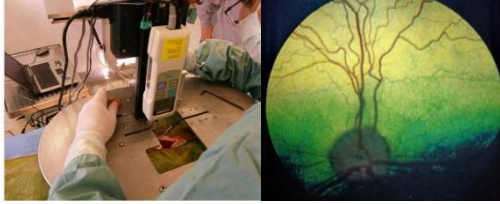

# Experimental facilities available

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**, USA

**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

**Oxford University**, UK

**Rottapharm**, Italy

**Sanofi Group** (Zentiva)

**Sunpharma**, India

**Univ Hospital Basel**, Switzerland

**University of Zagreb**, Croatia

**Triveritas**, USA/UK

**Univ of Medicine and Health Sciences,** Irland

**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**<br>**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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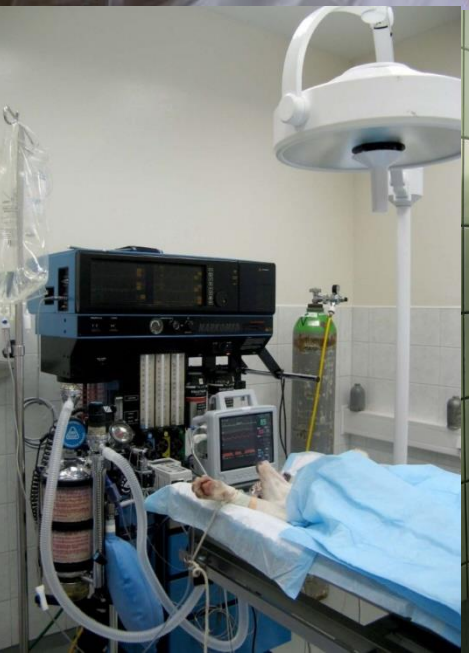

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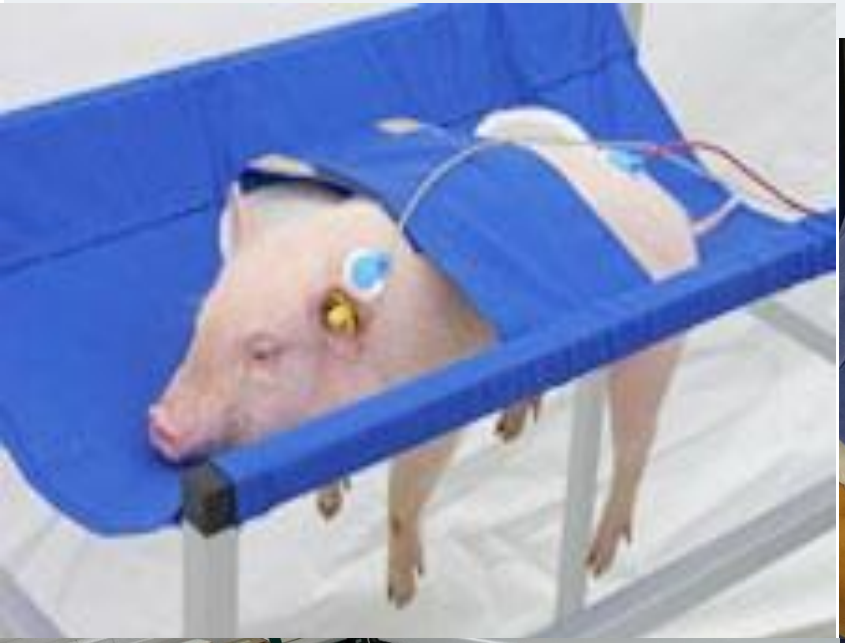

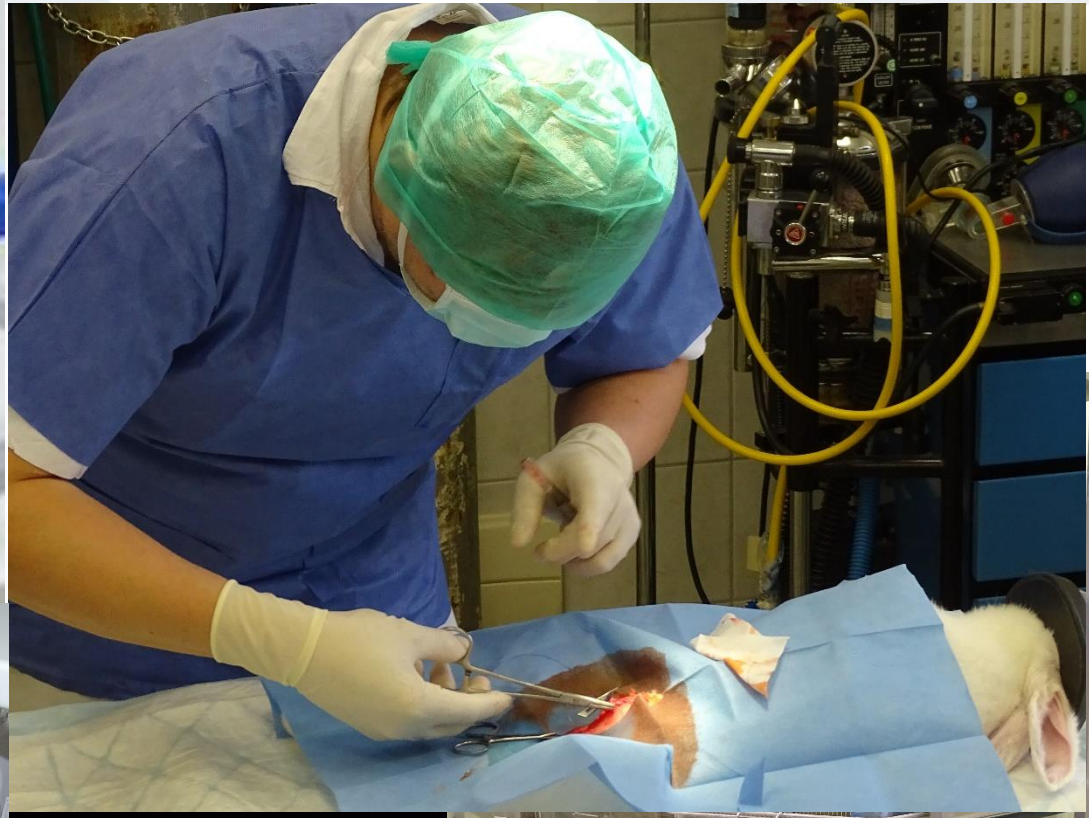

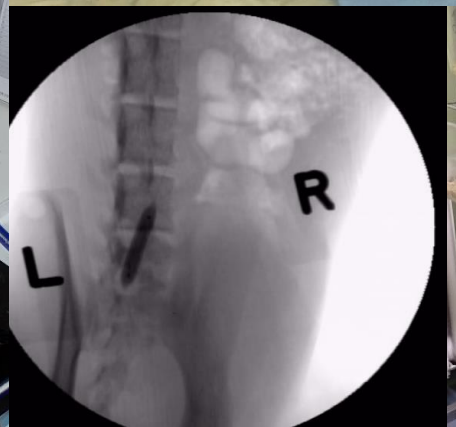


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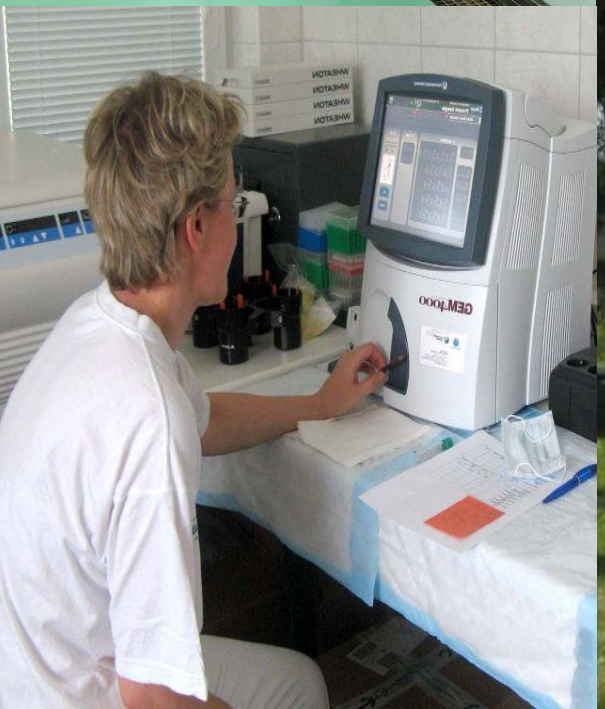


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CARDIOLOGY DISEASES

HUNTINGTON´S DISEASE MODEL

DIABETES / OBESITY MODEL

OPHTHALMOLOGY DISEASES

**PRECLINICAL RESEARCH AND DEVELOPMENT**

**COMPREHENSIVE PRECLINICAL TOXICOLOGICAL PROGRAM**

**ANIMAL MODELS OF SELECTED HUMAN DISEASES**

**ACCREDITED BREEDING FACILITY FOR LABORATORY ANIMALS**


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