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Center for Comparative Medicine

Tools for Research Support and Development,
with experience and quality.



ICIVET LITORAL

About the Center for Comparative Medicine

“Over 15 years providing technological support for biomedical research”

The general objective of the Center for Comparative Medicine (CMC) at the Faculty of Veterinary Sciences of the Universidad Nacional del Litoral “(Esperanza, Santa Fe, Argentina) is to do research with laboratory animals under international standards of ethics and quality regarding their use and care.

The CMC was established in August 1997 by teachers and researchers interested in the care and use of laboratory animals, primarily for research in veterinary science, medicine and biology. The CMC currently boasts with a total area of approximately 520 m² for production of different laboratory animals, biological testing, quality management and administrative offices. To this are added 300 m² of high complexity laboratories associated with the Center. Since March 2013, the CMC has become part of the Instituto de Ciencias Veterinarias del Litoral (Institute of Veterinary Sciences of Litoral) (ICiVet-Litoral), an Institute that belongs to the Scientific and Technical Research Council of Argentina (CONICET). Since 2016, an institution of the Scientific and Technological System in the country has been established as the first and only integrated Center that combines the certifications and qualifications correspondign to SENASA, ANMAT, ISO 9001 and GLP-OECD. The CMC has been a member of the National Bioterial System (NBS) of the Ministry of Science, Technology and Productive Innovation since 2014.

Activities at the CMC are focused on improving Animal and Human Health, through the provision of laboratory animals and the development of experimental models for improving products and biomedical procedures.

The team includes Veterinarians, Biologists, Biochemists, and graduates in Biodiversity and Biotechnology, as well as technicians specialized in the care of laboratory animals. The team thus covers different areas of the medical sciences such as pathology, microbiology, parasitology, pharmacology, toxicology, cell culture, immunology, imaging, fine chemistry, biochemistry, ethics and molecular biology, among others.

One of our key missions is to support qualified work for basic research, development, and quality control, for researchers and companies that require it.

As it is well known, laboratory animals are essential for most researchers working in the fields of biology, veterinary and medicine. In addition, laboratory animals are necessary for pharmacological and toxicological tests as well as for everything related to microbiology and physiology. On the other hand, we consider that respecting national and international standards on Ethics in Experimentation and Animal Welfare is essential. The work carried out at the CMC complies with the principles of international guidelines for research involving laboratory animals.



Quality Management

All records of the quality management system are available for on-site audit.

The CMC has implemented a Quality Management System certified according to the ISO 9001 standards and declared by the Argentine Accreditation Organization (OAA) in accordance with the requirements of Good Laboratory Practices (GLP) to conduct of non-clinical studies, with specific scope for pharmaceutical products. The Quality Management System, which is the result of the policy of quality defined by the Board of Directors of the CMC, includes the organizational structure, functions, activities, resources, staff training and necessary documentation to ensure that the services provided meet the expectations of customers in addition to legal and regulatory requirements related to the activity.

The functioning of the organization under a comprehensive Quality Management System provides control and forecast at the time of providing laboratory animals and carrying out services entrusted by third parties, thus lowering risks of disruptions during their performance and thus leading to an increase in the productivity of the organization and in the fidelity of our customers.

In addition, the CMC has very strict and specific procedures to ensure the confidentiality of the relationship with customers.

The CMC also has a measurement and monitoring system that allows the continuous improvement of procedures to detect and analyze possible problematic aspects and thus implement the necessary actions to correct the causes of problems. The organizational process includes periodic internal audits to each of the Areas that make up the CMC. In addition, clients make permanent audits to different processes within the CMC, an action that has led to many improvements in these processes.

The Quality Management System of the CMC is reflected on the following documents:

- Quality Manual
- Standard Operating Procedures (SOPs)
- Instruction Manual
- Instructional Charts
- Organization charts
- Records

The CMC periodically carries out internal microbiological quality controls of different processes and supplies. It also performs microbiological monitoring of laboratory animals by external laboratories. Trained staff of the institution regularly performs clinical (through necropsies and biochemical analyzes) and parasitological monitoring.





ANMAT

In 2007, the CMC adopted compliance with «Good laboratory practices» (GLP), which has been verified by the National Institute of Medicines (INAME) of the National Administration of Drugs, Food and Medical Technology (ANMAT Argentina), certifying compliance with ANMAT Provision (6344/96) referring to the «Regulation for Bioterios of laboratories elaborating medicinal specialities and/or analysis for third parties».



SENASA

Since 2008, the CMC is part of the National Network of Laboratories Authorized by the National Service of Food Quality (N° LR0139, SENASA, Argentina), for the supply of animals for laboratory and biological testing according to Res. 736/06. Besides, it has certifies compliance with Resolution 617/2002, referring to «Requirements, conditions and procedures for the technical qualification of laboratories holding production of animals to Animal Facility Centers, maintenances, and experimental sites».



IRAM - ISO 9001:2008

In 2014, the CMC has implemented and maintains a Management System which fulfills the requirements of the IRAM-ISO 9001 standard, under the registration number 9000-0006005, whose scope is «Raising of rats, mice and rabbits intended for activities of teaching and research in academic, scientific and business institutions».



Good Laboratory Practices (GLP)

The CMC has been declared by the Argentine Accreditation Organization (OAA) in accordance with Good Laboratory Practices (GLP-OECD) for conducting clinical studies. In particular the areas of expertise include toxicity, mutagenicity, toxicokinetics, pharmacokinetics and pre-clinical safety assessment of biotech and pharmaceutical products. Conformity Record with the GLP-018.



National System for Animal Facilities Centers

Since 2014, the CMC has been included as a member (ID 841) of the National System for Animal Facilities Centers, of the Ministry of Science, Technology and Productive Innovation.



Objetives:

The overall goal is an integrated approach to animal research laboratory under international standards

Overall aims.

- To produce high quality laboratory animals in sufficient numbers. To design, advise and execute biomedical assays, guaranteeing a high quality, to meet the requirements of different users.
- To ensure respect for national and international standards on the care and use of experimental animals.

Key aims.

- To encourage the development of basic and applied research on the use of animal models.
- To contribute to the generation of knowledge to improve the health and well-being of humans and animals.
- To provide technological support.
- To constitute a regional reference center and disseminate knowledge that highlights the importance of the use of experimental models in the study of biomedical sciences.
- To ensure respect for national and international standards on the care and use of animals for experimentation and other scientific purposes.
- To contribute to the integral formation of professionals in the Veterinary Sciences.
- To provide infrastructure and support for research and training of human resources within the scope of the Faculty of Veterinary Sciences of the Universidad Nacional del Litoral and researchers from other public and private institutions that require it.



Ethics and Welfare

The use of animals in research, teaching, and biological testing, is acceptable only if it contributes effectively to a better understanding of biological principles

Animal experimentation is one of the fundamental pieces in biomedicine, research projects, diagnostic tests and controls for pharmacological products. In its 11th Inter-American Meeting of 1980, the Pan American Health Organization (PAHO) expressed that: «countries which have achieved a breakthrough in the control of human and animal diseases are those that have established entities dedicated to a better development of the Science of Laboratory Animals».

The use of animals in research, teaching and biological testing is acceptable only if it contributes effectively to the understanding of fundamental biological principles or to the development of knowledge that we can reasonably expect to benefit humans or animals.

Animals should be used only when the researcher has already sought for an acceptable alternative. The continuous exchange of knowledge, literature review, and adherence to the principles of «Three Rs» of Russell-Burch (Replacement, Reduction, and Refinement) are other necessary conditions. Researchers who use animals should use the most humanitarian methods available, make that the number used is the smallest possible, and use the appropriate species for valid results.

The works carried out at the CMC comply with the principles of international guidelines for research involving animals. In addition, the CMC has an Advisory Committee of Ethics and Safety, which was created to ensure that the activities that involve the use of animals carried out at the Faculty of Veterinary Sciences of the Universidad Nacional del Litoral are conducted humanely and within the framework of international standards of ethics and biosecurity. Protocols and standard operating procedures held at the CMC are evaluated by this Committee.



Facilities of the CMC

In addition, there is an area of productive biological trials with cages and facilities for the management of large animals during clinical assays.

The CMC has 520 m² of covered space, integrating production areas of different animal species, bio-logical testing, quality management and several outbuildings for administration, maintenance and storage rooms.

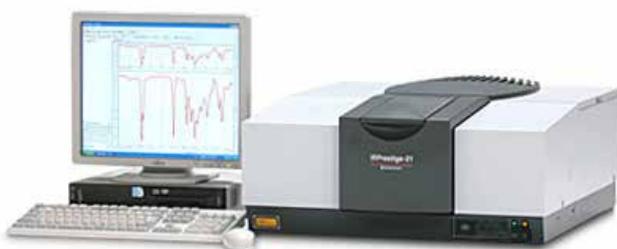
All the rooms, including those for both production and biological testing, have automated controls of temperature, illumination and air renewal with high efficiency filtering systems.

The production area has four rooms for breeding and stock, as well as changing rooms, laundries, preparation of materials and an independent storage room.

The area of biological testing has rooms for the maintenance of different species, boxes for the housing, isolation and quarantine of large animals, and laboratories for general procedures and initial processing of samples. There is also an administrative area, with a meeting room with a video conference system, an archive with a system of protection against fires, and research and development offices. The facilities have security systems that allow the permanent and remote monitoring of all the areas of the CMC by using high resolution cameras, as well as control equipment and environments through specific sensors that ensure the immediate response in case of any kind of emergency. The building is integrated with that of the Faculty of Veterinary Sciences of the Universidad Nacional del Litoral, in direct relation with its Laboratories of High Complexity, which work in association. This allows us to address comprehensively the development of experimental protocols.

These fully installed laboratories include:

- Laboratory of Applied Cellular and Molecular Biology
- Laboratory of Clinical Trials
- Laboratory of Pharmacology and Toxicology
- Laboratory of Food Analysis
- Laboratory of Image Analysis
- Laboratory of Microbiology
- Laboratory of Parasitology
- Laboratory of Histology and Pathological Anatomy
- Area of Radiology and Diagnostic Imaging
- Operating room of High Complexity





Animal Facilities Center:

- Air conditioning system with efficiency filtering.
- Individually Ventilated Cages (IVC systems).
- Animal transfer stations with protection class II.
- Biological Safety Hoods.
- An emergency power system.
- Autoclave.
- System of automatic monitoring of environmental conditions.

- Chison 8300 vet Digital Portable Ultrasound.
- Emptying system of beds of high security.
- Ultrafreezers.
- High Performace Computer Servers.
- Integral System for building safety.
- Mindray portable color doppler ultrasound Z6Vet Scanner.

Analytical equipment:

- Equipments for cellular and molecular biology (real time thermocyclers, digital microscopes, etc) for diagnosis and health monitoring.*
- LC-MS/MS system composed of a liquid chromatograph Shimadzu UFLC XR and a Triple Quadrupole Gas Chromatograph Mass Spectrometer AB Sciex Q-Trap 3200.
 - Near Infrared (NIR) Spectrophotometer Shimadzu Prestige.

- Clinical chemistry autoanalyzer Metrolab 2300 plus.
- Mindray hematology autoanalyzer BC-2800Vet.
- Cellular and tissue culture laboratory fully equipped for in vitro assays.
- Attune NxT Acoustic Focusing Flow Cytometer.



Equipment for High Complexity Testing



Attune NxT Acoustic Focusing Flow Cytometer.

It allows detecting the presence of molecules and materials of interest by immunofluorescence techniques, fluorescent sensors or fusion of fluorescent proteins, both in fixed particles and in living cells, which makes it possible to address, among others, the study of cellular dynamic processes and identifying cells populations in specific models.



Histopathological Studies.

A histopathology laboratory is available, with veterinary pathologists, with extensive specific training in the area and advanced technology that includes automatic microtomes and microscopes equipped with digital imaging systems. In addition, a panel of more than 300 antibodies allows to deepen the resolution of findings through immunohistochemistry techniques.

Mass Spectrometry.

A LC-MS/MS system consisting of a Shimadzu UFLC XR liquid chromatograph and a triple quadrupole mass spectrometer with linear ABI cheex trap Q-Trap 3200. It allows the identification and quantification of molecules in different matrices with very high specificity and sensitivity.



Hematology Autoanalyzer.

Mindray Automatic Analyzer BC-2800 Vet, which allows to perform all the analytical stages of hematology under GLP and the monitoring of the Quality Management Area of the CMC. This equipment has validated routines for different species and allows the automatic and small volume analysis of 19 hematological biomarkers in different toxicology and safety tests.



Color Doppler Ultrasound.

Mindray Doppler Ultrasound Z6Vet, with high frequency linear and microconvex transducers allows high resolution images to be entered that facilitate correct data collection in different studies. It is useful in the exploration of organs and structures in lab animals, including abdominal, small parts, cardiovascular and ophthalmological studies.

Besides, it allows to evaluate the speed, direction and spectral frequency, as well as the indices of resistance and pulsatility of the blood flow. These benefits are essential during the assessment of tumor development and response to treatments in vivo models applied to oncology, among many other benefits.



Digital electrocardiograph.

A Cardiocom Digital CC12Der device allows to respond to international standards that require the evaluation of cardiotoxicity in preclinical trials of new medicines intended for use in humans. It works with seven simultaneous leads, manual and automatic scanning, and a specific software for laboratory animals that automates the analysis of the different segments of the electrocardiogram.

Animals

The CMC has its own production of genetically certified mice, rats and rabbits and has registered its own international laboratory code (Cmedc) at the Institute for Laboratory Animal Research (The National Academies of Sciences, Engineering, and Medicine, USA). In addition, it has areas available for the maintenance of other species often used in biological trials such as poultry, pigs and cattle.



Rats.

Wistar/Cmedc Strain: Strain of own production, currently stabilized with an endocria superior to F30.

Mice.

BALB/c Cmedc: Strain derived from animals of the Jackson Laboratory (USA), currently with an endocrine superior to F15.

Rabbits.

New Zealand Breed: animals produced in our Center, coming from plants acquired in the best cabins of the country, with genetic certification granted by the Sociedad Rural Argentina.



Monitoring and quality control



Periodically, the microbiological monitoring of supplies (bed, food and water) as well as animals from the production and stock colonies is performed to evaluate different health aspects. In addition, microbiological and genetic monitoring is carried out in external laboratories, worldwide, to evaluate the presence of frequent pathogens in laboratory animals and the genetic quality of ours. The controls performed include the specific pathogens and parasites listed in the corresponding reports that are recognized for causing disease or compromising health status. Opportunistic agents are also detected, however, some of them are tolerated on the basis of international guidelines. The production data of all species are under a system of good practices, with archived records that allow the traceability of all the animals used or sold.

Services and Offers

The main services include the sale of animals and the performance of tests with different complexity including the production of hyperimmune sera, specific protocols and research projects, complex multidisciplinary trials, surgeries, immunogenicity studies, in vitro tests, comprehensive preclinical evaluation of biopharmaceuticals, among others.

The CMC also seeks to provide users with a scope to carry out all the work in the place, assigning specific rooms to each test and thus avoiding the need to move the animals to areas that do not meet the corresponding standards or their manipulation by unqualified personnel.

In recent years it has provided services to more than 40 research and development groups based in National Universities and Institutes from CONICET and to more than 30 companies in the pharmaceutical and health sector. These users come from different parts of the country and abroad, having the necessary logistics for the transport of animals and samples.





Services performed by specific laboratories of the Faculty of Veterinary Science, Universidad Nacional del Litoral.

- Provision of animals for the development of research and teaching activities.
- Advice for the installation of Animal Facilities Centers and Test Areas.
- Design and execution of biological tests according to national and international standards (SENASA, ANMAT, OPPT, OECD, FDA, EMA, EPA, ICH, Pharmacopoeias, etc).
- Planning and development of preclinical trials of high complexity according to national and international standards (ANMAT, FDA, EMA, ICH, ANVISA).
- Planning and development of field clinical trials in farm animals, according to national and international standards (SENASA, VICH).
- Biological evaluation of medical devices according to noma ISO 10993.
- Development of specific experimental models of high complexity.
- Quality control biological activity of drug according to pharmacopoeias.
- Safety tests.
- Pyrogen test.
- Acute, subacute and chronic toxicity tests.
- Biocompatibility studies.
- Tolerance and sensitization tests.
- Studies of homogenization, reproductive toxicology and teratogenicity.
- Pharmacokinetic and toxicokinetic studies.
- In vitro assays.
- Provision of homogenization.
- Preparation of polyclonal sera.
- Molecular biology techniques.
- Biochemical studies.
- Pharmacological studies.
- Toxicological studies.
- Histopathological studies.
- Immunologic studies.
- Experimental surgeries.

The CMC has a Quality Management System certified by ISO 9001 for the provision of animals, and the tests are performed in accordance with Good Laboratory Practices (GLP-OECD). This system includes the organizational structure, functions, activities, resources and documentation necessary to ensure that the services provided meet customer expectations in addition to regulatory and legal requirements related to the activity. All records are available for on-site auditing.

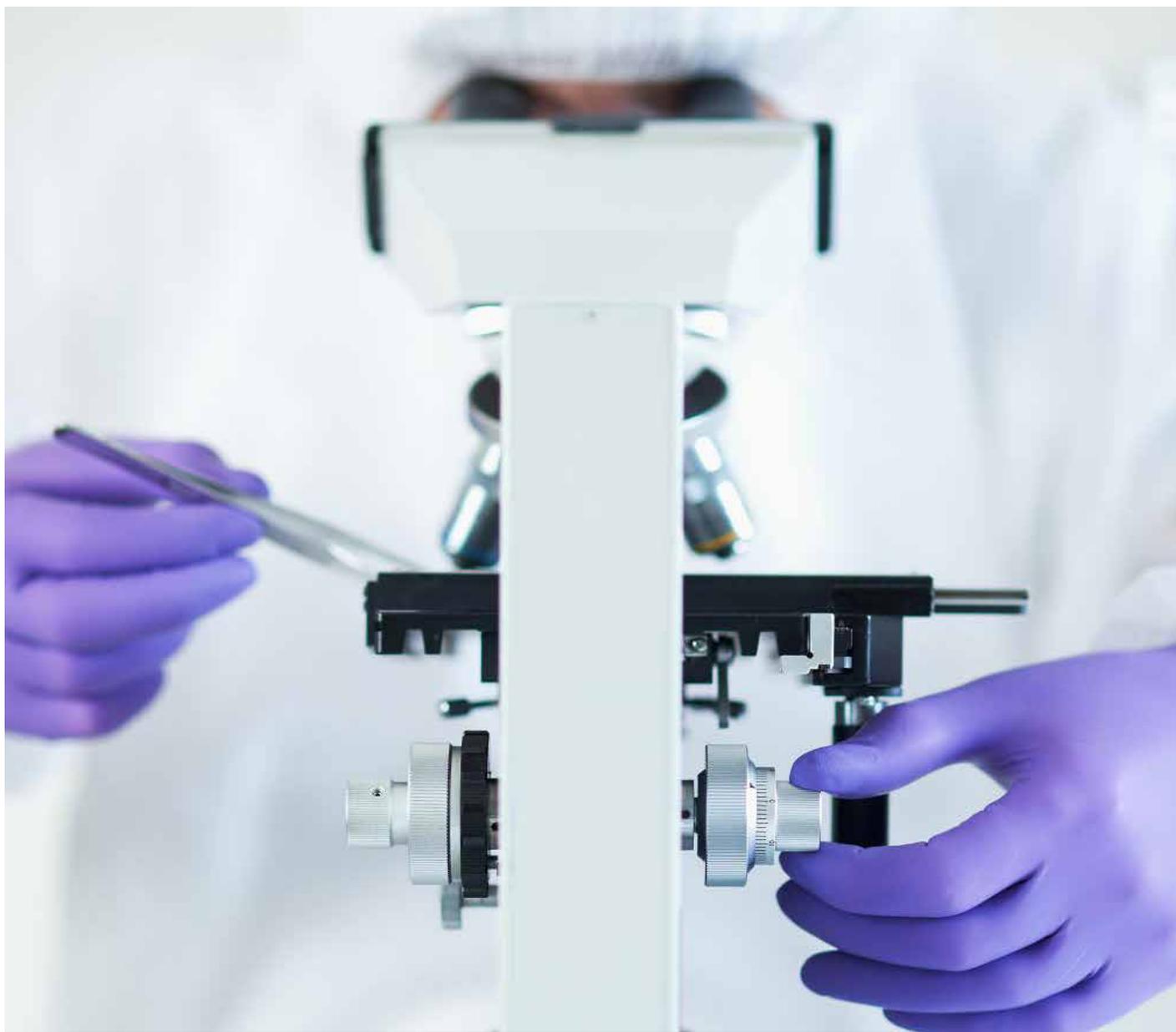
Research and transfer

Research and transfer projects are carried out within the CMC, and they have allowed for the constant growth of the Center's operational capacities and the generation of knowledge in the field of comparative medicine. Several of these projects have been in collaboration with companies from the pharmaceutical sector of the country and abroad.

Among the projects that have been implemented until 2013, or which are currently being developed, the following stand out:

- *Proyect «Centro de Experimentaciones Biológicas y Bioterio (FCV-UNL): Adecuación a Normas Nacionales», financed in the framework of the Application for Registration Change of Scale, Course of Action for Technology Transfer 2006. Universidad Nacional del Litoral.*
- *Proyect «Adopción de Buenas Prácticas de Laboratorio (BPL) en el Centro de Experimentaciones Biológicas y Bioterio (FCV-UNL): herramientas imprescindibles para el aseguramiento de la calidad», financed in the framework of the Application for Registration Change of Scale, Course of Action for Technology Transfer 2007. Universidad Nacional del Litoral.*
- *Proyect «Validación de métodos alternativos en el Centro de Experimentaciones Biológicas y Bioterio (FCV-UNL): nuevas herramientas para la investigación aplicada al desarrollo», financed in the framework of the Application for Registration Change of Scale, Course of Action for Technology Transfer 2008. (Res CS 292/08). Universidad Nacional del Litoral.*
- *Proyect «Certificación de Buenas Prácticas de Laboratorio (BPL) en el Centro e Experimentaciones Biológicas y Bioterio (FCV-UNL): herramientas imprescindibles para el aseguramiento de la calidad», financed in the framework of the Application for Registration Change of Scale, Course of Action for Technology Transfer 2009. Universidad Nacional del Litoral.*
- *Proyect «Aplicación de los principios de Buenas Prácticas de Laboratorio (BPL) a los sistemas informáticos del Centro de Experimentaciones Biológicas y Bioterio (FCV-UNL)», financed in the framework of the Application for Registration Change of Scale, Course of Action for Technology Transfer 2009. Universidad Nacional del Litoral.*
- *Proyect «Desarrollo de una plataforma analítica para estudios preclínicos bajo los lineamientos de las Buenas Prácticas de Laboratorio», financed in the framework of the Application for Registration Change of Scale, Course of Action for Technology Transfer 2010. Universidad Nacional del Litoral.*
- *Proyect «Plataforma tecnológica para el desarrollo y producción de nanotransportadores inteligentes para fármacos», financed by the Agency for Scientific and Technological Promotion, within the framework of the Application for Nanotechnology FS 2011, through the Argentine Sectoral Fund (FONARSEC).*
- *Proyect «Generación de una plataforma tecnológica bajo Buenas Prácticas de Manufactura (BPM), para la industria farmacéutica dentro del Centro de Experimentaciones Biológicas y Bioterio», financed in the framework of the Application for Registration Change of Scale, Course of Action for Technology Transfer 2010. Universidad Nacional del Litoral.*
- *Proyect «Desarrollo de métodos alternativos para la evaluación de nuevos materiales de uso biomédico en Medicina Humana y Veterinaria», financed under the application for the strengthening of the innovation capacities of the Santa Fe Province's Production System. State Secretariat for Science, Technology and Innovation (SECTeI) of Santa Fe.*
- *Proyect «Programa de Acreditación de Laboratorios en Ciencia y Tecnología», financed by the Agency for Scientific and Technological Promotion. Res MINCyT 428/12.*
- *Proyect «Desarrollo de una plataforma de producción de proteínas recombinantes de interés veterinario y sus aplicaciones.», financed in the framework of the Application for Registration Change of Scale, Course of Action for Technology Transfer 2012. Universidad Nacional del Litoral.*
- *Proyect «Centro de Medicina Comparada: Consolidación de una plataforma tecnológica de alta complejidad para el análisis de fármacos y productos biotecnológicos», financed by the Agency for Scientific and Technological Promotion, within the framework of the FINSET 2015 application for the Argentine Technological Fund (FONTAR). Fondo de Financiamiento para Actividades de Promoción, Fomento y Gestión Tecnológica (CONICET).*





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