



ANIMALS IN PHARMACEUTICAL RESEARCH

A responsible approach

CONTENTS

- P03** | OUR APPROACH TO ANIMAL RESEARCH
- P04** | USING ANIMALS IN RESEARCH AND DEVELOPMENT
- P06** | GLOBAL STANDARDS
- P08** | OUR PRINCIPLES ON THE USE OF ANIMALS
- P10** | 3R – REPLACE, REDUCE AND REFINE
- P12** | A CULTURE OF CARE
- P14** | SPECIFIC ETHICAL ISSUES
- P16** | ETHICAL REVIEW AND AUDITING
- P19** | GOVERNANCE SYSTEM
- P20** | STAKEHOLDER ENGAGEMENT





NOVO NORDISK'S BIOETHICS POLICY

In Novo Nordisk we will discover, develop and produce biological medicines with respect for people, animals and the environment. This means that we will:

- continuously improve our performance
- promote bioethical awareness in Novo Nordisk
- operate by high ethical global standards in research involving people, animals, human materials and gene technology
- require adherence to high ethical standards by our external partners, contract research organisations and suppliers, and monitor their performance
- engage in stakeholder dialogue and partnerships helping us to deal with ethical dilemmas
- comply with laws, relevant requirements and act in accordance with international conventions.

WHAT IS BIOETHICS?

At Novo Nordisk, bioethics is the term we use for all ethical issues related to the use of life science technologies for the discovery, development and production of pharmaceutical products. It is of utmost importance to Novo Nordisk that, in the process of bringing a new product to market, we carefully consider the ethical implications of our research and development activities and are attentive to societal concerns. We focus on ethical issues related to clinical, stem cell and animal research and the use of human biosamples and gene technology in research and development.

MADS KROGSGAARD THOMSEN

*Executive vice president and chief science officer,
Novo Nordisk*

We only use animals when there is no viable or legal alternative and continuously seek to reduce the number of animals we still need to use.



OUR APPROACH TO ANIMAL RESEARCH

For a long time to come, the use of animals will continue to be necessary in pharmaceutical research. While it is desirable to replace the use of live animals in procedures with other methods not entailing the use of live animals, the complicated interaction between a pharmaceutical product and a living organism cannot be replicated completely in a test tube. In the interests of protecting human life, the law requires all new drug candidates to be tested in live animals before they can be tested in people. However, it is also a legal requirement in the EU to consider the replacement, reduction and refinement (the 3Rs) in all aspects of the care and use of animals.

So, while we recognise that we cannot eliminate the use of animals completely, we are replacing the use of live animals with

tissue cultures and cell-based methods whenever possible. We facilitate and promote the advancement of alternative approaches and expect that new emerging technologies will make it possible to obtain even more important information without the use of live animals.

We only use animals when there is no viable or legal alternative and continuously seek to reduce the number of animals we still need to use.

We do everything we can to ensure that the animals are treated well and to refine our procedures so that the animals experience the least distress. We also apply high global standards in the housing and care of the animals and maintain state-of-the-art conditions for all animals in our care.

We are attentive to societal concerns regarding the use of animals in research. We continuously engage with and learn from our stakeholders.

We report on our use of animals annually on our website and welcome many guests to our animal housing facilities every year – including students, animal welfare groups and journalists.

We strive to be open and honest about everything we do, and I therefore hope that you will find this brochure of interest.



Mads Krogsgaard Thomsen

*Executive vice president and chief science officer,
Novo Nordisk*

USING ANIMALS IN RESEARCH AND DEVELOPMENT

Research using animals has led to many medical advances and treatments

Animals have been used in medical research and development since 300 BC and have played an important role throughout the history of the life sciences. In the 20th century, research using animals led to many medical advances and treatments, including insulin for the treatment of diabetes. In 1921, insulin was tested for the first time in a dog with diabetes. This revolutionised the treatment of diabetes and, subsequently, Novo Nordisk – today a world leader in diabetes care – was founded.

To this day, the use of animals in research is essential for all pharmaceutical companies in the processes of discovery of new pharmaceutical products. To protect humans, it is in fact a requirement by the authorities that new products are tested in live animals before they can be tested in people. Furthermore, companies are required to provide appropriate data regarding

efficacy, safety and toxicology from testing in both animals and people before the authorities can approve a new product.

Supporting the 3Rs

Novo Nordisk uses live animals in the discovery and development of new products when there is no viable or legal alternative. To protect the animals and continuously improve their welfare, the company has for many years actively supported the principles of the 3Rs: to reduce the number of animals used to obtain the same results, refine the conditions for the animals and replace the animals by using *in vitro* methods. The 3Rs were first introduced in 1959 by Professor William Russell and Rex Burch*. These principles have since become widely accepted internationally as the basic principles guiding animal use in research, teaching and testing. Novo Nordisk integrates these principles in all its processes and procedures.

* The 3Rs were introduced in the publication *The Principles of Humane Experimental Technique*, written by Professor William Russell and Rex Burch.

TOTAL NUMBER OF ANIMALS PURCHASED



Numbers

Several factors determine how many animals Novo Nordisk needs in a given year, such as the number, nature and development phases of new pharmaceuticals, regulatory requirements and

ANIMALS PURCHASED

2011-2014

NUMBER AND SPECIES OF ANIMALS PURCHASED

Species	2014				Novo Nordisk total			
	In-house DK	In-house outside DK	In-house total	External contractors	2014	2013	2012	2011
Mice	23,396	9,199	32,595	1,854	34,449	38,186	33,831	31,363
Transgenic mice	9,545	0	9,545	1,472	11,017	12,121	13,722	10,012
Rats	9,633	401	10,034	5,560	15,594	19,050	22,890	22,491
Transgenic rats	974	0	974	0	974	384	225	190
Gerbils	39	0	39	24	63	0	199	113
Guinea pigs	0	0	0	292	292	0	50	208
Hamsters	14	0	14	20	34	142	34	6
Rabbits	372	0	372	202	574	1,124	691	535
Pigs	428	0	428	390	818	1,177	1,170	953
Dogs	12	87	99	275	374	238	434	344
Primates	0	0	0	344	344	240	355	186
Total	44,413	9,687	54,100	10,433	64,533	72,662	73,601	66,401

Since 1994, Novo Nordisk has been reporting annually on the number and species of animals purchased by the company and used by external contractors. The accuracy, completeness and reliability of the information provided are ensured through internal control measures and external independent audits.

the development of validated new methods that can reduce or replace the use of animals. In the process of developing a new medicine, animal research is still necessary, in particular to assess the safety of a new medicine before it is tested in humans participating in clinical trials.

Novo Nordisk continuously strives to reduce the number of animals but, due to the significant growth of the company and its increased research activities, the total number of animals needed is likely to increase.

More than 90% of the animals used by the company are mice and rats, and these are used in the initial stages of drug discovery. In the later stages of each project, a relatively small number of larger animals, such as rabbits, pigs, dogs and non-human primates, are used. It is required by law that a drug candidate be tested in two different animal species, one of them not being a rodent, before it is allowed to be tested in humans.

GLOBAL STANDARDS

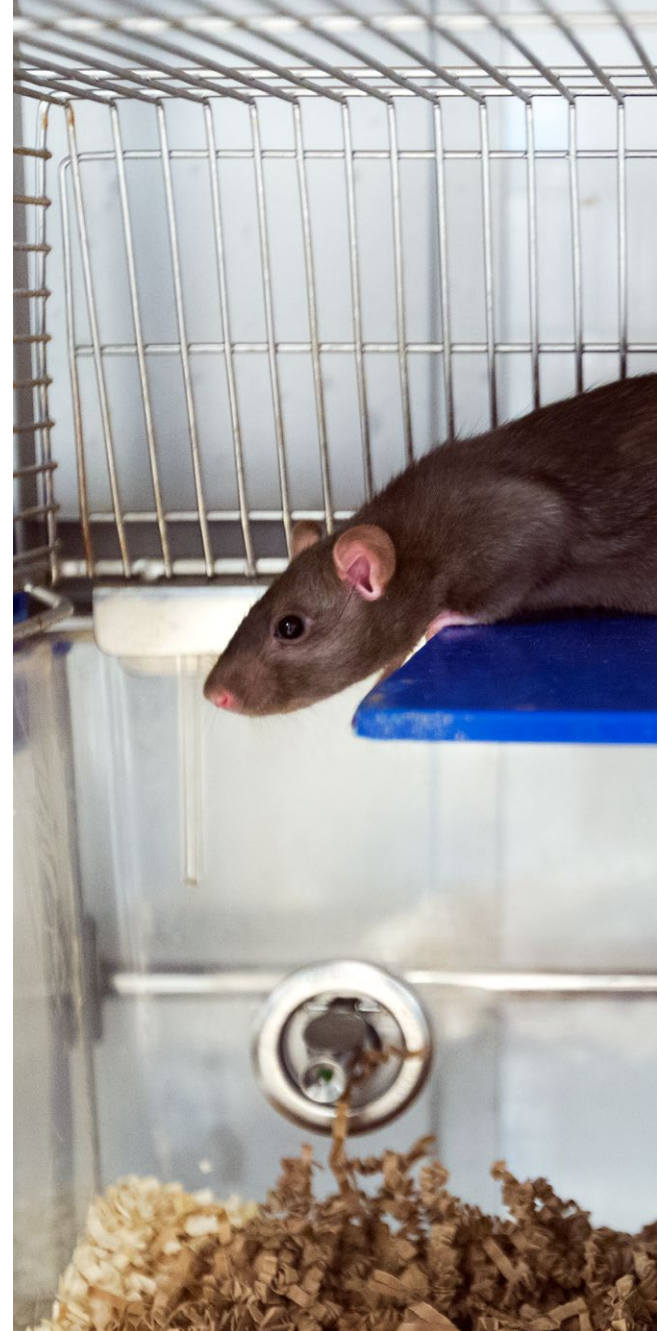
Attitudes towards animals vary with national perceptions and regulation. Novo Nordisk has therefore established a set of principles and global standards for the housing and care of animals, reflected in a series of Standard Operating Procedures (SOPs) and internal guidelines.

The global standards comply with the latest and most comprehensive international guidelines, the Council of Europe's Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (ETS No. 123, Appendix A) revised and adopted in 2006. These guidelines form the basis for Directive 2010/63/EU of the European Parliament and of the Council on the protection of animals used for scientific purposes, which regulates the use of animals in research and takes the physiological and behavioural needs of the animal species into account. To ensure that the company's global standards are applied globally, internal

training of employees working with animals (e.g., veterinarians, laboratory technicians, animal caretakers) is conducted across Novo Nordisk's global sites and a staff exchange programme for employees from different sites has been established.

External contractors

Presently, Novo Nordisk performs approximately 80% of the company's animal studies at its own research facilities. The remaining 20% are performed by external contractors, who must comply with Novo Nordisk's principles and ETS No. 123, Appendix A. A monitoring guide and an audit process on the use of animals at external contractor facilities have been established to ensure that all external contractors comply with Novo Nordisk's global standards and principles on the use of animals. The company visits, monitors and approves all external contractors prior to initiation of





GLOBAL STANDARDS

Ethical issues have no borders. Novo Nordisk has therefore established global standards and has global requirements for its business partners and suppliers.

a project in order to review conditions and procedures. Any deviations from this guideline are described and evaluated. Finally, an animal welfare statement is signed by both parties. "We do not permit any animal studies to be performed by 'non-approved' external contractors. If only minor changes are required, we work with the external contractors to bring their levels up to our expectations. This collaboration and dialogue has led to improved conditions at several external contractor facilities," says veterinarian Stine Øvlisen, head of 3R Management and Strategy at Novo Nordisk. "It is our belief that this is the best way to facilitate improvements in animal welfare around the world."

In Denmark, where the majority of Novo Nordisk's research and development takes place, each type of experiment is subject to prior approval by the Animal Experiments Inspectorate under the Ministry of Environment and Food of Denmark.

OUR PRINCIPLES ON THE USE OF ANIMALS

To ensure uniform standards the following principles must be adhered to throughout Novo Nordisk and all our external collaborators including contract laboratories, research laboratories, partners and suppliers

Novo Nordisk considers the use of animals to be essential for the discovery, development and production of pharmaceutical and medical products.

Ethical considerations and animal welfare are given high priority at Novo Nordisk. As an integral part of our approach to animal testing, we are constantly looking for new ways to replace, reduce and refine the use of animals for testing.

Animals will be used only where no available and acceptable alternatives exist.

- All activities involving animals must be conducted strictly in accordance with present legislation
- Alternatives to animal experiments must be used whenever possible
- Transgenic animals may be used for testing and experiments when this model is justified
- Animals bred specifically for experimental purposes must be used unless special conditions are in evidence
- Housing, husbandry and transportation of animals must as a minimum comply with internationally approved standards
- Housing conditions must take into consideration the special needs for the animals species in question
- Housing, husbandry and care of animals must be undertaken by personnel having received adequate and relevant education. The level of education must be documented
- Health control should be supervised by a veterinary officer experienced in regard to laboratory animals
- Transportation of animals must be as lenient as possible, taking into consideration the special needs for the animal species in question
- All precautions must be taken to reduce suffering and distress
- Procedures for monitoring and evaluation of the wellbeing of the animals as well as treatment must be implemented
- At Novo Nordisk records are kept updated on the type of experiment, animal species and number of animals used in accordance with the authorities' and the requirements of Novo Nordisk. The number of animals used internally as well as on facilities run by external collaborators will be published on [novonordisk.com](https://www.novonordisk.com).



PRINCIPLES

Novo Nordisk has established guiding principles to govern the company's use of animals in research and development.

3R – REPLACE, REDUCE AND REFINE

Before new pharmaceutical products can be studied in people, they need to be investigated in animals for efficacy, safety and toxicology, as it is not yet possible to examine the complex interactions in a living organism solely by the use of cell cultures and tissues.

Animals are only used in research and development at Novo Nordisk when no alternative exists. The use of animals in the early phases of the company's drug discovery and development has been reduced by applying tissue cultures, cell-based and other non-animal models. In addition, Novo Nordisk reviews animal models on a continuous basis for replacement with *in vitro* methods and uses human cells and tissues instead of living animals whenever possible.

Strategic 3R efforts

Novo Nordisk has long questioned the necessity of using animals (*in vivo* tests) in drug release testing. Strategic efforts were initiated in 1999 with the aim of removing the authorities' man-

datory requirement for quality-testing marketed products in living animals. A group of dedicated employees set out to prove that a total of 11 *in vivo* tests of marketed products could be replaced by non-animal tests. Despite challenges and setbacks, the group worked with great determination, performing extensive research and collaborating with authorities around the world. Eventually, official bodies agreed to remove obsolete tests and evaluate the consistent quality of our marketed products using new laboratory assays developed by Novo Nordisk and certified by the authorities.

By 28 November 2011, the publicly declared goal was finally achieved, and Novo Nordisk conducted the last *in vivo* tests for quality control of its marketed products. Novo Nordisk has subsequently implemented procedures to ensure that no more animal tests will be required by the authorities for quality tests of already approved products before they are released to market.





A MILESTONE IN ANIMAL ETHICS

After a decade of research and close collaboration with authorities around the world, as of November 2011 Novo Nordisk no longer tests the quality of batches of marketed products on live animals.



A CULTURE OF CARE

3R department

Being a growing global company with a commitment to the 3Rs and a desire to continuously do more is not a simple task. As a consequence, Novo Nordisk decided to take a more strategic approach to the 3R activities by establishing a centralised department in 2015. 3R Management and Strategy drives 3R innovation with a focus on animal welfare and improving laboratory animal science. The department contributes to internal awareness and education and an even deeper integration of 3R considerations in decision-making processes. Furthermore, the department will engage in dialogue with our key stakeholders and enter into collaborations and partnerships.

Housing of animals

It is important to Novo Nordisk to act with due respect for the animals used in research. The company has a longstanding history of abiding by a 3R culture, and we set annual goals based on the 3Rs. We have developed new and high animal welfare standards in a unique partnership with the Danish Animal Welfare Society.

HOUSING STANDARDS

Novo Nordisk's housing standards consider the physiological and behavioural needs of the animals. The company has successfully implemented these standards for all animals housed at its facilities.

The implemented standards for housing animals have significantly improved the welfare of the animals. The standards take the physiological and ethological (behavioural) needs of the animals into consideration and are based on valuable input from ethologists and the animal caretakers. Improvements include group housing of rabbits in large pens, larger cages and hides for the rodents and large exercise areas for the dogs and pigs.

Novo Nordisk established these standards before such standards were incorporated into the revised Council of Europe's guideline on the protection of animals used in research and development as well as

3R AWARD

The Novo Nordisk 3R Award is given to employees who bring Novo Nordisk's commitment to the 'Reduction, Refinement and Replacement' (3R) principles into action.

new Danish legislation and later on in EU Directive 2010/63/EU. All employees involved with animals used in research receive training in animal welfare, care and handling. Scientists, laboratory technicians, animal caretakers and veterinarians cooperate on refining not only the housing and care of the animals but also the scientific procedures used in relation to the investigation of new drug candidates.

Novo Nordisk 3R Award

To highlight the importance of a constant focus on animal welfare, Novo Nordisk has established a 3R Award where all employees in research and development are encouraged to participate. The first Novo Nordisk 3R Award event was hosted in 2009. At the award ceremony, employees who reduce the numbers of animals, replace their use or improve the conditions for animals used in research are recognised and invited to share and exchange ideas. An external jury of animal welfare specialists selects the winning project and a People's Choice Award winner is selected by the audience attending the event. The finalists' 3R initiatives as well as a video of the event are published on novonordisk.com.



SPECIFIC ETHICAL ISSUES

The use of animals in research and development is a concern for Novo Nordisk – as it is for many people – but some issues demand particular attention. These include the use of disease models, transgenic animals and non-human primates.

Disease models

Novo Nordisk is committed to the development of treatments for chronic conditions and their complications. In the search for better treatments within diabetes, obesity, haemophilia and growth hormone disorders, specific animal models are used. Novo Nordisk acknowledges the concerns surrounding the use of animal models reflecting human disease and maintains a keen focus on the need to use such models. We continuously strive to refine the models when used, in an ongoing dialogue between scientists, the Ethical Review Council and employees from the laboratory animal science units.

Transgenic animals

The animal models used by Novo Nordisk include transgenic animals reflecting human diseases to obtain the best scientific and predictive information about the effect and safety of new pharmaceutical products prior to testing them in people. “We recognise that inducing human disease in animals may cause discomfort to the animals. We therefore provide the animals with appropriate care. Furthermore, when animals are used for research purposes, we continuously define humane endpoints in order to minimise discomfort to the animals,” explains veterinarian Jan Ottesen, vice president of Laboratory Animal Science at Novo Nordisk.

Prior to engaging in the use of transgenic animals, Novo Nordisk has to obtain a permit from the authorities and from the internal Ethical Review Council.





Non-human primates

The use of non-human primates in research and development is questioned by many people on ethical, welfare and conservation grounds. Novo Nordisk only uses non-human primates when no other acceptable alternative exists. Only a relatively small number of non-humans primates are used to evaluate certain drug candidates for efficacy and safety prior to testing in humans and only after prior internal ethical review of each individual protocol. All of Novo Nordisk's research using non-human primates is performed by external partners, who are chosen based on their specialisation in the housing, care and use of non-human primates, and the company works closely with these partners to ensure the highest possible ethical and welfare standards and monitors their performance.

ETHICAL REVIEW AND AUDITING

The company has taken further steps to ensure the well-being of all animals used globally. Among these is the review of animal studies performed at or on behalf of Novo Nordisk by the internal Ethical Review Council (ERC) established in 2002.

ERC

Members of ERC must cover different areas of expertise and stay up-to-date on animal ethics, legislation, 3R initiatives, study design and statistics in order to provide guidance to and sharing best practice with researchers.

All research that uses animals, whether carried out at Novo Nordisk or on behalf of the company by external contractors or collaborators, requires review and approval by the internal ERC. A description of the aim of the study, justification for the choice of animal species, the number of animals required and the study design are all put before the ERC.

The review process then focuses on the following issues:

1. Adherence to Danish and European legislation
2. Adherence to Novo Nordisk's principles on the use of animals
3. The principles of the 3Rs
4. Cost/benefit analysis of the study in question as well as assessments of humane endpoints, pain and distress to the animals.

The ERC has the means to challenge, change or even reject protocols if ethical concerns about the animals' welfare and use arise. "The ERC enters into dialogue with our scientists and is invited onboard very early in the projects, to ensure ethical considerations are included and delays are avoided," explains Stine Øvlisen, Chairman of the ERC and head of 3R Management and Strategy at Novo Nordisk, "but sometimes decisions made by the ERC increase costs or prolong the initiation of a study."

The strong dialogue between the ERC, the scientists and our collaborators leads to constant improvements. Novo Nordisk believes that the potential downsides of the internal ethical review of animal studies are more than outweighed by more reliable scientific results, the value of better practices and, which is of paramount importance, improved animal welfare.

Audits

Novo Nordisk's animal facilities and procedures are frequently assessed by both internal and external auditors. We undergo announced and unannounced audits, including from the Danish Animal Experiments Inspectorate, to check that the company lives up to current regulations and the conditions set out in our permits. In addition, Novo Nordisk invites external experts, including animal welfare groups, to challenge its performance and propose new areas for the company's attention.

ETHICAL REVIEW COMMITTEE

Novo Nordisk's Ethical Review Committee ensures that the company lives up to all its bioethical commitments, including adherence to the principles of the 3Rs (Reduce, Refine and Replace).





GOVERNANCE SYSTEM

Novo Nordisk was one of the first pharmaceutical companies to establish a comprehensive governance system for bioethics including activities related to the use of animals in research.

Senior management support

Novo Nordisk's senior management exercises stringent governance responsibilities regarding the ethical use of animals. This is reflected both in the organisational structure, where Laboratory Animal Science is recognised as an independent VP area, and in the systematic approach the company has developed to address bioethical issues.

Social and Environmental Committee

Novo Nordisk's bioethical work is governed by the Social and Environmental Committee, mandated and chaired by Novo Nordisk's Executive Management. The Committee is responsible for the company's policy and strategy on bioethics.

Global Bioethics Management

A dedicated department, Global Bioethics Management, and a virtual crossfunctional

team of 70-80 employees work to ensure that Novo Nordisk's business activities are ethically sound and that the company continuously improves its bioethical performance.

R&D Bioethics Council

The Research and Development Bioethics Council strengthens the coordination of bioethical activities and ensures synchronicity, knowledge and information sharing. The Council is established by R&D Executive Leadership team and prepares and suggests new initiatives, develops and implements new policies and guidelines, and supervises Novo Nordisk's handling of bioethical issues worldwide.

3R department

See page 12.

Ethical Review Council

See page 16.

Expert groups

Five expert groups address Novo Nordisk's major inherent bioethical issues. One of them is animal

research. Expert groups ensure that emerging issues are addressed, set annual goals and ensure implementation.

Bioethics anchors

A global network of bioethics anchors has been established. The anchors provide a global perspective, ensure alignment and incorporate local contributions to Novo Nordisk's proactive bioethical work.

Training and guidance

For many years, Novo Nordisk has run an in-house training course on the use and welfare of animals in research and development for all employees involved in this area. "Core components of the course are the ethical implications and dilemmas," says veterinarian Jan Ottesen, vice president of Laboratory Animal Science at Novo Nordisk. "External experts in animal ethics and animal welfare participate as guest lecturers." Animal welfare officers provide daily guidance to employees to ensure compliance with ethical and welfare standards.

STAKEHOLDER ENGAGEMENT

Novo Nordisk is committed to sharing, and learning from, best practices. We continue to learn from our tremendously valuable stakeholder dialogues and partnerships. “We recognise the importance of input from external stakeholders and our employees,” explains Lise Holst, director of Global Bioethics Management at Novo Nordisk. “We listen to ideas and concerns and take them into account when setting annual goals and developing new initiatives and policies.” Novo Nordisk frequently meets with various stakeholders, such as animal welfare groups, governments and regulators, researchers, students and journalists, to discuss animal ethics and welfare issues. The company participates in seminars, symposiums and conferences to learn and share best practice.

Public/private partnerships

Novo Nordisk is one of the stakeholders supporting The Danish 3R-Center established in late 2013 by the Ministry of Environment and Food of Denmark. A unique collaboration between the

Ministry, the pharmaceutical industry and animal welfare organisations, the aim of The Danish 3R-Center is to focus on alternatives to animal testing and on creating better conditions for laboratory animals. The company is also a member of partnerships supporting the 3Rs, for example the European Partnership for Alternative Approaches to Animal Testing (EPAA), a joint initiative by the European Commission and a number of companies and trade federations to promote the development of the 3R initiatives, and the In Vitro Testing Industrial Platform (IVTIP) comprising 42 companies from different sectors. In addition, the company is one of the founders of the Centre for Applied Laboratory Animal Research (CALAR), a Danish partnership between academia and industry, where scientists from universities and private research institutions work together on projects to improve animal housing conditions and refine experimental procedures for the benefit of both the animals and animal caretakers.

Animal welfare organisations

Novo Nordisk engages with animal welfare organisations, including the Danish Animal Welfare Society, the UK’s Royal Society for the Prevention of Cruelty to Animals (RSPCA) and the Universities Federation for Animal Welfare (UFAW) to ensure improved housing conditions for animals used in research and development.

Industry associations

Novo Nordisk is a member of the laboratory animal working group of the Danish Association of the Pharmaceutical Industry (Lif). The Association advocates for legislation and administrative procedures that adequately balance the needs and welfare of animals and humans. The Association is a member of the European Federation of Pharmaceutical Industries and Associations (EFPIA), with several working groups focusing on issues related to the use of animals. Novo Nordisk takes part in this work to share best practices with its European colleagues.

JAN OTTESEN

*Veterinarian and vice president of Laboratory
Animal Science at Novo Nordisk*

Every animal life counts, and we see it as our obligation to continuously do our utmost to reduce, refine and replace the use of animals.



TAKE A CLOSER LOOK

Ethical considerations are part of everyday life in research and development at Novo Nordisk. This brochure is part of a series of brochures on bioethical issues. You can download these brochures and find further information on Novo Nordisk's approach to the use of animals in research on Novo Nordisk's bioethics webpages: **novonordisk.com/rnd/bioethics**

Contact

Novo Nordisk welcomes feedback, comments and suggestions on this brochure. Send your comments to: **bioethics@novonordisk.com**

Novo Nordisk A/S
Novo Allé
2880 Bagsværd
Denmark
Tel +45 4444 8888
novonordisk.com



PurePrint® by KLS
Produced 100% biodegradable
by KLS Graftek Hus A/S