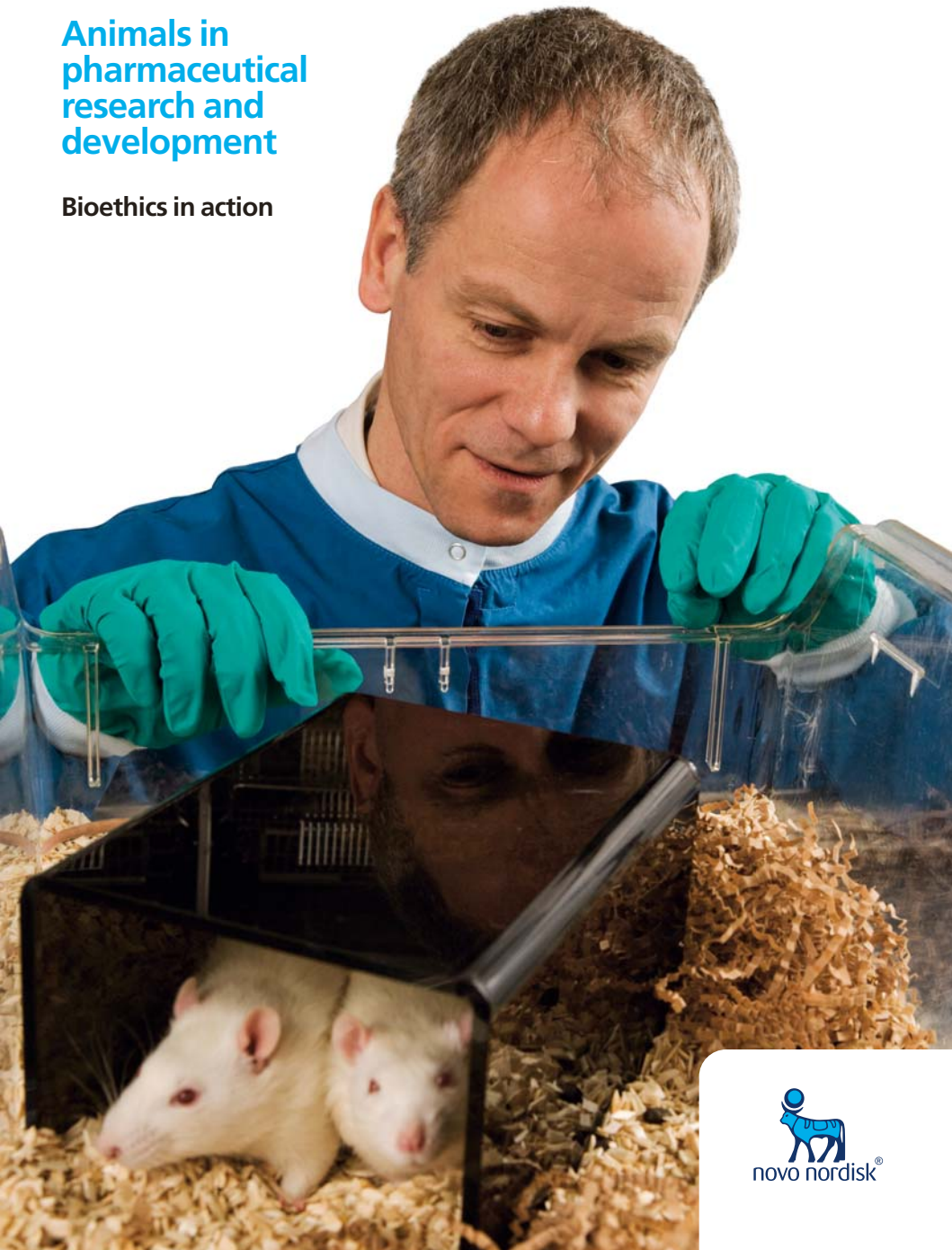


Animals in pharmaceutical research and development

Bioethics in action



What is bioethics?

At Novo Nordisk bioethics is the expression used for all ethical issues related to the use of life science technologies in the discovery, development and production of pharmaceutical products. This covers the ethical aspects of the use of human biological material, animals and gene technology in research, and clinical trials.

Novo Nordisk Bioethics Policy

In Novo Nordisk we will continuously improve our bioethical performance.

This means that we will:

- Promote bioethical awareness throughout the company
- Establish and ensure high ethical standards for:
 - experiments on live animals
 - clinical trials and use of human material
 - gene technology
 - our external partners, contract research organisations and suppliers, and monitor their performance
- Engage in stakeholder dialogue and partnerships, and report on our performance
- Live up to the spirit, values and principles and content of relevant conventions, laws and requirements

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Novo Nordisk's approach to bioethics

For a long time to come we will need to use animals in research and development. The complicated interplay between a pharmaceutical product and a living organism will never be replicated completely in a test tube – which is why it is a legal requirement that all new drugs are tested in living animals before they can be tested in people.

So, while we recognise that we cannot eliminate the use of animals completely, we are committed to doing everything we can to minimise the number of animals used and to ensure that the animals we do use are treated well, and that Novo Nordisk's global standards are applied.

We are working continuously to find alternatives to using animals in research and development, such as tissue cultures and cell-based methods. In addition, Novo Nordisk is a pioneer of the new discipline called biosimulation, which involves computer models to simulate human biology as closely as possible.

The animals are not used in research for most of their lifetime. Therefore, we pay special attention to the housing and care of the animals and have established state-of-the-art housing conditions for all animals housed at Novo Nordisk.

We are attentive to societal concerns about bioethical issues such as the use of animals in research and development. We continuously engage with and learn from our stakeholders. We report on our use of animals in annual reports and welcome many guests to our animal housing facilities every year – including employees not working with animals, students, animal welfare groups and journalists.

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



Mads Krogsgaard Thomsen
Executive vice president and chief science officer
Novo Nordisk

Using animals in research and development

Animals have been used in medical research and development since 300 years 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.

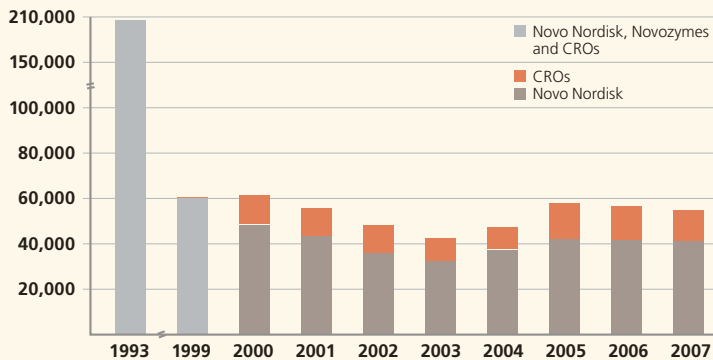
To this day, the use of animals in research is essential for all pharmaceutical companies in the processes of discovery, development and production of new pharmaceutical products. In fact, it is a requirement from the authorities that new products are tested in living animals before they can be tested in people. Companies are required to provide appropriate data regarding efficacy, safety and toxicology from testing in both animals and people before the authorities will approve a new product.

Novo Nordisk uses live animals in the discovery and development of new products when there is no viable or legal alternative. However, the company strives to reduce the number of animals used and between 1993 and 1999 Novo Nordisk reduced the number of animals purchased by almost 70%. Since then, the company has kept the number at approximately the same level (see graph on opposite page) even though its research activities have increased each year. It is expected that new emerging technologies will make it possible to obtain even more important information without the use of living animals.

Several factors determine how many animals Novo Nordisk will use in a given year, such as the number, nature and development phases of research projects, regulatory requirements and the development of validated new methods that can reduce or replace the use of animals. More than 90% of animals used by the company are mice and rats, and these are used in the initial stages of drug discovery. A relatively small number of larger animals, such as rabbits, pigs, dogs and non-human primates, are used in the later stages of each project. Presently, Novo Nordisk performs approximately 75% of the company's animal studies at its own research facilities in Denmark. The remaining 25% of its animal studies are performed by external contractors.



Total numbers of animals purchased by Novo Nordisk and contract research organisations (CROs)



Between 1993 and 1999, Novo Nordisk succeeded in reducing the total number of animals purchased in research and development by almost 70%. Since then, Novo Nordisk has been able to keep the numbers at approximately the same level despite increasing research activities year on year.



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

Global standards

Novo Nordisk has established principles and global standards for housing and care of animals. The 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 take the physiological and ethological (behavioural) needs of the animal species into account and have been implemented in Danish legislation.

To ensure these standards are applied globally, the company has developed a series of Standard Operating Procedures (SOPs) including, in 2006, an SOP on the housing of animals at Novo Nordisk. A monitoring guide and an audit process on the use of animals at external contractors ensure compliance with Novo Nordisk's principles and Council of Europe legislation when studies are outsourced. In Denmark, where the majority of Novo Nordisk's research and development takes place (approximately 75%), each type of experiment must receive prior approval by a public body called the Council on Animal Experimentation under the Danish Ministry of Justice.

The company has taken further steps to ensure the well-being of all animals used. "For example, there is no legal requirement in Denmark for an internal ethical review committee – yet we have established such a committee and review all animal studies," says Lars Friis Mikkelsen, laboratory animal veterinarian and chair of the Ethical Review Committee at Novo Nordisk.

Novo Nordisk actively supports the principles of the 3Rs: reduce the number of animals used to obtain the same results, refine the living conditions for the animals or replace the animals by using *in vitro* methods. The 3Rs were first introduced in 1959 in the publication *The Principles of Humane Experimental Technique*, written by Professor William Russell and Rex Burch. These principles have 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.

Novo Nordisk's principles on the use of animals

To ensure uniform standards the following principles are adhered to throughout Novo Nordisk and by all its external collaborators including contract laboratories, research laboratories, partners and suppliers:

- 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 animal 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 considerate 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 well-being of the animals as well as treatment must be implemented
- Records must be kept updated on the type of experiment, animal species and number of animals used in accordance with the authorities' and Novo Nordisk's requirements. The number of animals used internally as well as on facilities run by external collaborators will be published in the Novo Nordisk annual report.

Any planned deviations from these principles must be approved in advance by the Novo Nordisk Environment, Bioethics and Occupational Health & Safety Committee.



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





Over the past decade Novo Nordisk has succeeded in achieving regulatory approval to remove tests using animals to check the potency and quality of the company's approved products, significantly reducing the number of animals used.

Reduce and Replace

New drugs need to be investigated in animals for efficacy, safety and toxicology before they are studied in people, and 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 and cell-based methods. 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.

Novo Nordisk is a pioneer of the new discipline called biosimulation, which involves computer models that simulate the biological processes in humans as closely as possible: "As an initiator and partner in the EU Network of Excellence in Biosimulation (BioSim), we have succeeded in getting more than 200 of the EU's best scientists to focus on how biosimulation can contribute to drug development and support the principles of the 3Rs," explains Morten Colding-Jørgensen, scientific advisor at Novo Nordisk and professor in biosimulation at The Technical University of Denmark.

The company has also successfully challenged the authorities on the appropriateness of using animals to check products that have already gained regulatory approval. Of the original ten tests, eight have been totally removed or replaced with *in vitro* assays developed by Novo Nordisk, and the number of animals used in the only two remaining tests has been considerably reduced. Furthermore, procedures have been established to ensure that any new product, once it has received approval, will not subsequently need to be tested on animals.

Refine

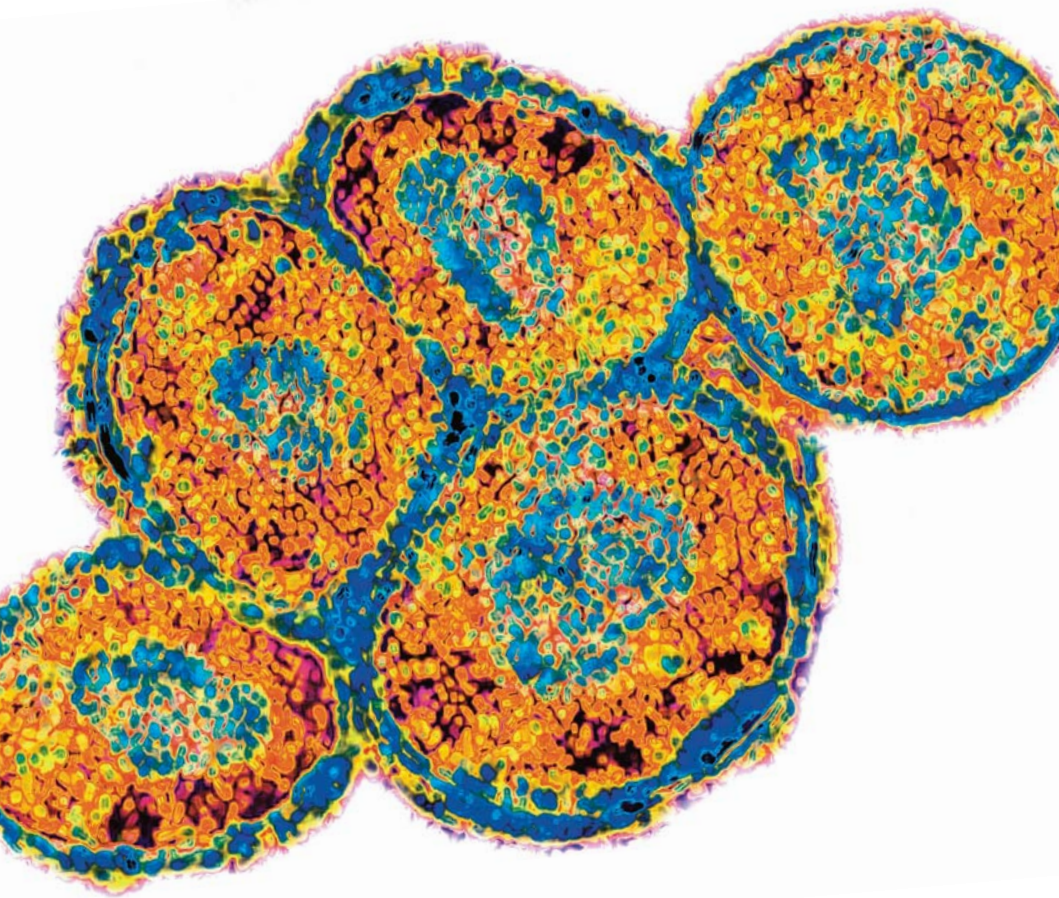
It is important to Novo Nordisk to act with due respect for the animals used in research and development, and the company has developed high animal welfare standards. In addition, all employees who are involved in this area receive training in animal welfare, care and handling.

Novo Nordisk has, in a unique partnership with the Danish Animal Welfare Society, established new standards for housing animals, which improves animal welfare and minimises stress. The improved housing standards take into consideration the physiological and ethological (behavioural) needs of the animals 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 outdoor areas for the pigs. Novo Nordisk established these standards before the incorporation of such standards in the revised Council of Europe's guideline on the protection of animals used in research and development as well as new Danish legislation.

Approximately 25% of all animal studies performed by Novo Nordisk are outsourced and the company ensures that all external contractors do also comply with its global standards and Principles on the use of animals. Novo Nordisk visits, monitors and approves all external contractors prior to initiation of a project to review conditions and procedures. Monitoring is based on the Council of Europe's guideline for accommodation and care of animals. Any deviations from this guideline are described and evaluated. "We do not accept any animal studies to be performed at 'non-approved' external contractors. If only minor changes are required, we work with the external contractors in order to help them bring their levels up to meet our expectations. This collaboration and dialogue has led to improved conditions at several external contractors," says Lars Friis Mikkelsen, laboratory animal veterinarian at Novo Nordisk. "It is our belief that this is the best way to facilitate improvements in animal welfare around the world." Finally, an animal welfare statement is signed by both parties.



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



Genetic modification of cells and organisms presents a unique opportunity to gain insight into human diseases.

Dealing with specific 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 animal models including transgenic animals and the use of non-human primates.

Animal models

Novo Nordisk uses animal models including transgenic animals to reflect human diseases and to obtain the best scientific and predictive information about the effect and safety of its new pharmaceutical products prior to testing in people. “We recognise that the induction of human diseases in animals may cause discomfort to the animals. We therefore provide the animals with suitable care and define humane endpoints, that is choosing the earliest endpoint that is compatible with the scientific objectives of the research,” explains veterinarian Jan Ottesen, head of the Animal Unit at Novo Nordisk.

Transgenic animals

Novo Nordisk uses transgenic animals as models for human diseases when testing new products. Transgenic animals are animals whose hereditary properties have been permanently modified by the introduction of recombinant DNA into their germ cells. The company proactively shares information about why and how animals are modified genetically and how they are used.

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-human primates are used by Novo Nordisk and only after prior internal ethical review of each individual protocol. Non-human primates are used to evaluate certain drugs for efficacy and safety prior to testing in humans and to model certain human diseases. All of Novo Nordisk’s research using non-human primates is performed by external partners, who are specialised in the housing, care and use of non-human primates. “The company works closely with these partners to ensure the highest possible ethical and welfare standards and monitors their performance,” explains Lars Friis Mikkelsen, laboratory animal veterinarian at Novo Nordisk. “In addition we have established a group including internal and external animal welfare experts to develop and share best practices regarding husbandry and care of non-human primates.”

Ethical review and assessments

All research that uses animals, whether carried out at Novo Nordisk or on the company's behalf by external contractors, requires review and approval by its internal Ethical Review Committee. 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 Committee. 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; and 4) cost/benefit analysis of the study in question as well as assessments of humane endpoints, pain and distress to the animals. The Committee has the means to challenge, change or even reject protocols if ethical concerns about the animals' welfare and use arise.

"Decisions made by the Ethical Review Committee do sometimes increase cost," explains Lars Friis Mikkelsen, laboratory animal veterinarian at Novo Nordisk. "But we believe that this economical downside is more than outweighed by the value of better practices, more reliable scientific results, and of paramount importance, improved animal welfare."

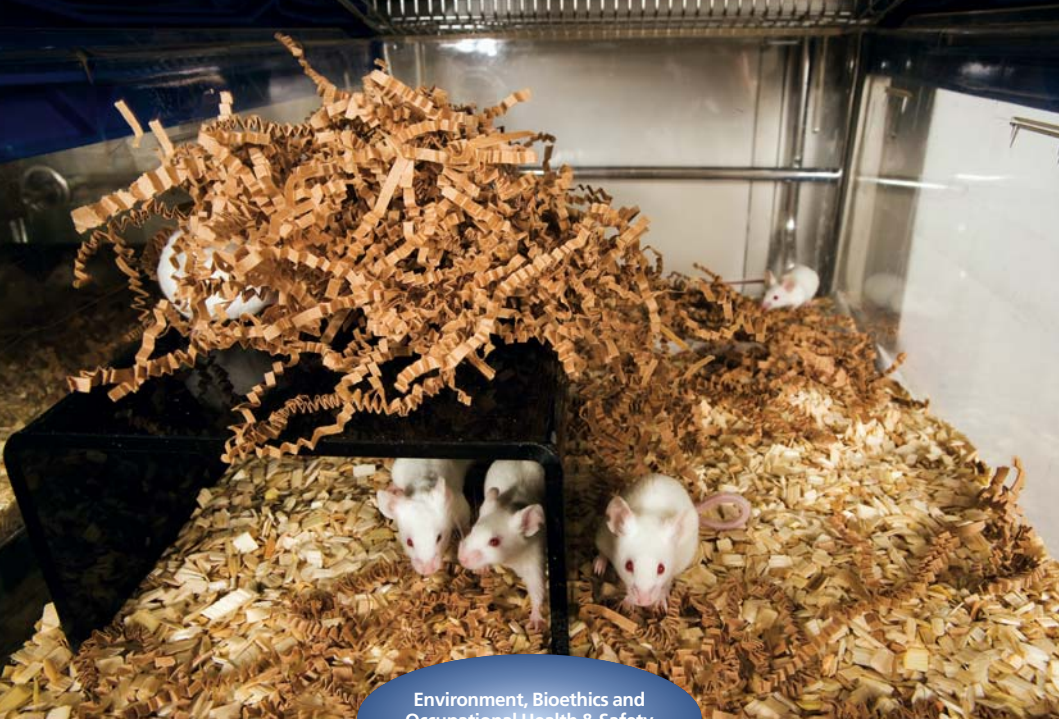
Novo Nordisk's animal facilities and procedures are frequently assessed by both internal and external auditors. Authorities, including the Danish Animal Experiments Inspectorate, pay announced and unannounced visits to its facilities to check that the company lives up to current regulations and conditions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

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 information provided are ensured through internal control measures and external independent assurance.

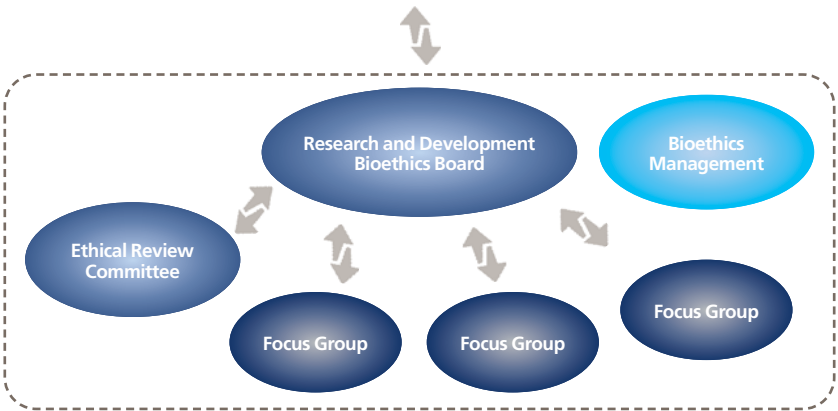


Rex L Burch (left) and William M Russell, pictured in 1995, the scientists who formulated the 3Rs principles of reduction, refinement and replacement. "The pharmaceutical and cosmetic industry can make great contributions to the progress of the 3Rs and I am happy to say that they have already achieved much in that direction," said Professor Russell.

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).



Environment, Bioethics and Occupational Health & Safety Committee



Novo Nordisk was one of the first pharmaceutical companies to establish a comprehensive governance system for bioethics. The system also covers its activities related to the use of animals in research and development.

Governance system

Novo Nordisk has developed a systematic approach to dealing with bioethical issues. A dedicated department, **Bioethics Management**, and a virtual cross-functional team of 50–70 employees work to ensure that Novo Nordisk's business activities are ethically sound.

Environment, Bioethics and Occupational Health & Safety Committee: The company's bioethical work is governed by the Environment, Bioethics and Occupational Health & Safety Committee, mandated and chaired by Novo Nordisk's Executive Management. The Committee is responsible for the company's policy and strategy on bioethics.

Bioethics Board: The Research and Development Bioethics Board strengthens the co-ordination of bioethical activities and ensures synchronicity, knowledge and information sharing. The Board prepares and suggests new initiatives, develops and implements new policies and guidelines, and supervises the company's handling of bioethical issues worldwide.

Ethical Review Committee: The Ethical Review Committee ensures that any animal study performed by or on behalf of Novo Nordisk is carefully reviewed from an ethical perspective and integration of the principles of the 3Rs. The members are academic and technical employees – some of whom work with animals while some do not – to ensure a broad perspective when considering the animals' welfare.

Focus groups: Focus groups and other relevant groups are established when a specific bioethical issue needs special attention. Presently, Novo Nordisk has focus groups within the areas of the use of animals in biological product control, monitoring of external contractors and non-human primates.

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. "Central elements of the course are the ethical implications and dilemmas," says veterinarian Jan Ottesen, head of the Animal Unit 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

Over the years, Novo Nordisk has learnt from stakeholder dialogue and partnerships. “We recognise the importance of input from our employees and external stakeholders,” explains Lise Holst, director of Bioethics at Novo Nordisk. “We listen to all these voices and take concerns and ideas into account in our review of existing bioethical guidelines and in the formulation of new initiatives and policies.”

Animal welfare organisations: Novo Nordisk works 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. In addition, the company is a member of 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.

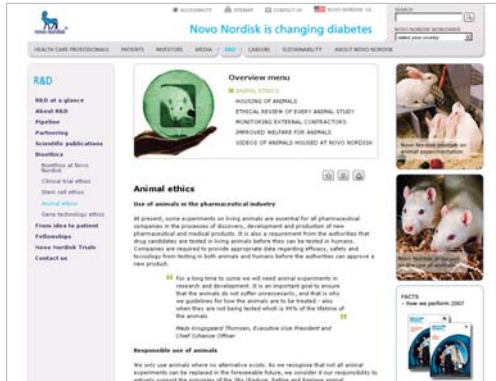
Public/private partnerships: Novo Nordisk is one of the founders of the Centre for Applied Laboratory Animal Research (CALAR), a Danish partnership between academia and industry. Scientists from universities and private research institutions work together on projects to improve animal housing conditions and refine experimental procedures for the benefit of both the animals and animal caretakers.

Consensus platforms on alternatives: Through Lif, Novo Nordisk is represented on the Danish Consensus Platform for 3R Alternatives to Animal Experimentation (DACOPA) where representatives from Danish animal welfare groups, ministries, industry and academia work together to promote the implementation of the 3Rs in Denmark. DACOPA is a member of the European Consensus-Platform for Alternatives (ecopa), which brings together national platforms to promote 3R alternatives throughout Europe.



Novo Nordisk frequently meets with various stakeholders such as non-governmental organisations (NGOs), inter-governmental organisations (IGOs), governments and regulators, researchers, students and journalists to discuss bioethical issues. The company participates in seminars, symposiums and conferences to share knowledge and views.

Access to information



novonordisk.com/science/bioethics

Take a closer look

Bioethical considerations are part of everyday life in research and development at Novo Nordisk. Now a film provides a closer look at the company's search for better treatments. The documentary *Three days – searching for better treatment* follows three employees on a pivotal day for their projects and shares their reflections on the spirit of R&D at Novo Nordisk. The film explains the long and difficult road from idea to patient, where ethical issues are an inevitable part of the journey. View or request the film and accompanying booklet at Novo Nordisk's bioethics website.

Bioethics at your fingertips

Further information on Novo Nordisk's approach to bioethics, including its use of animals in research and development, and footage of animal housing, can be found on the company's dedicated bioethics website. The website aims to offer interested parties easier access to information on the company's approach and performance on a full range of bioethical issues.



“It is of the utmost importance that, in the process of developing a new medicine, we carefully consider any bioethical issues that arise. This includes the welfare of animals used in research and development, the safety of participants in clinical trials, the prudent use of gene technology and our impact on the environment and society.”

Mads Krosgaard Thomsen

Executive vice president and chief science officer, Novo Nordisk



Novo Nordisk welcomes feedback, comments and suggestions on this brochure as part of our ongoing dialogue and engagement with stakeholders.

Send your comments to:
Lise Holst, director, Bioethics Management
bioethics@novonordisk.com

Novo Nordisk A/S

Novo Allé
2880 Bagsværd
Denmark
Tel +45 4444 8888

novonordisk.com

