

## Setting global standards for animal welfare monitoring of external contractors

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### Abstract

Novo Nordisk, a healthcare company and world leader in diabetes care, is committed to actively implement the principles of the 3Rs.

Since approximately 25 percent of all animals are used externally it is important to ensure uniform standards at all these external contractors, i.e. contract research organisations, research laboratories and partners, as well as animal suppliers. They must all comply with "Novo Nordisk Principles on the Use of Animals" and they are animal welfare monitored prior to study initiation and with frequent intervals. The monitoring is based on the revised guideline from the Council of Europe's Appendix A of ETS No. 123, and all deviations from this guideline are described and evaluated by the end of the monitoring and an animal welfare statement is signed by both parties.

The conclusions from the animal welfare monitoring might have economical impact; e.g. demands for environmental enrichment and larger cages, but we believe that this is counterbalanced by the benefit of a global standard, bilateral exchange of experience, broader public acceptance, better animal welfare, and more reliable scientific results.

The paper will discuss lessons learned and the impact and benefits of performing animal welfare monitorings of external contractors worldwide.

**Keywords:** animal welfare, animal welfare monitoring, ethical review, external contractor, global standard

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### Introduction

At present, some experiments on living animals are essential for all pharmaceutical companies in the processes of discovery, development and production of new pharmaceutical and medical products. It is also a requirement from the authorities that drug candidates are tested in living animals before they can be tested in humans. Companies are required to provide appropriate data regarding efficacy, safety and toxicology from testing in both animals and humans before the authorities can approve a new product.

Novo Nordisk only uses animals where no alternatives exist. As we recognise that not all animal experiments can be replaced in the foreseeable future, we consider it our responsibility to actively support the principles of the 3Rs (Reduce, Refine and Replace) by integrating these principles in all our processes and procedures.

When animals are used their welfare is given high priority and attention in several ways. Novo Nordisk has initiated and developed new improved housing and care standards for all animal species used in-

house, based on the natural behaviour and needs of these animals (Ottesen JL et al., 2002). We perform ethical reviews on all studies before they are initiated; staff is trained in animal welfare, and we perform animal welfare monitorings at all external contractors as well as at our animal suppliers to ensure that they follow Novo Nordisk global housing standards for animals.

We think that the improved conditions mainly reflect an increased focus and interest among scientists and staff and a general trend within the society, but also when we perform follow-up visits, we hear and see that conditions at some places have been fundamentally improved inspired by our previous dialogue and suggestions for better animal welfare.

Conclusions from global animal welfare monitorings and decision points from the Ethical Review Committee might have some negative economical impacts, e.g. demands for bigger cages, fewer animal pr. cage or provision of environmental enrichment. At Novo Nordisk we believe, that these

economical cons are more than balanced by the pros: bilateral exchange of experience, more reliable scientific results, broader public acceptance and always, of paramount importance, improved animal welfare.

### **Ethical review of all animal study**

All animal experiments carried out at Novo Nordisk, or on our behalf by external contractors, require ethical review and approval by our internal Ethical Review Committee. The committee has reviewed all applications to the Danish authorities to get licenses to perform animal studies at our own animal facilities since 2002 and all protocols for external studies since 2006.

Novo Nordisk performs approximately 75% of our animal studies at our own research facilities in Denmark. Before any of these studies are undertaken an application for the specific animal studies must be sent to the Ministry of Justice for legal and ethical approval. In addition, our internal Ethical Review Committee reviews and approves these applications before they are sent to the authorities.

Novo Nordisk has established an assessment and monitoring procedure to ensure global animal welfare standards for all animals used in-house and ex-house. Animal studies planned to be performed by contractors are described in study protocols. They must all be reviewed and approved by our Ethical Review Committee before these animal studies can be initiated.

There is no legal requirement in Denmark for an internal ethical review committee. It was established as our way of ensuring, 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 (Reduce, Refine and Replace).

The Ethical Review Committee has the means to challenge and change or even reject the study protocols or the application whenever ethical concerns about the animals' welfare and use arise.

The ethical review process is focusing on the following issues: 1) Adherence to Danish and European legislation and guidelines presently setting the highest ethical standards globally, 2) Adherence to Novo Nordisk Bioethics Policy, 3) The principles of the 3Rs, and 4) Cost/benefit analyses of the experiment in question as well as assessments of humane endpoints and possible pain and distress to the animals. This includes justification of the choice of animal model, the number of animals required to test the given hypothesis and the study design.

The committee meets monthly and the members of the committee represent study directors, animal technicians, laboratory technicians, animal welfare officers, animal care technicians, a biostatistician, and

a lay member to ensure that the animals' welfare is taken into broad consideration.

### **The animal welfare monitoring**

Novo Nordisk uses external contractors, contract research organisations and research collaborators, like universities and other scientific research partners, for external animal studies which we do not have the capacity or expertise to carry out at Novo Nordisk.

We visit every external contractor before any animal studies can be initiated and do follow-up visits; we perform an animal welfare monitoring and the external contractor must live up to our standards to be approved. We discuss animal welfare issues and see how the animals are housed and cared for which give us a good impression of the actual animal welfare standard.

Furthermore, it enables us to make sure that all animals used by us are housed according to our expectation and standards. We also discuss the education and training of the employees working with the animals to ensure that the personnel working with the animals have the adequate training and experience.

The animal welfare monitoring is performed by a veterinarian with experience in regards to animal welfare. It is mandatory that the monitor has performed animal welfare monitoring before and is familiar with relevant national and international legislation and guidelines as well as Novo Nordisk standards. Additionally, the monitor must not be involved in the actual study.

In order for Novo Nordisk to accept an external contractor, all the animals used by us must be housed and cared for according to the revised guideline from the Council of Europe's Appendix A of ETS No. 123, approved in 2006 and the "Novo Nordisk Principles on the Use of Animals". This guideline takes the natural behaviour and needs of the animal species into account and is the latest and most comprehensive international guideline, which has already been implemented in the revised and very strict Danish legislation.

The conclusion of the animal welfare monitoring is based on the completed monitoring report which includes issues in relation to law/guidelines, personnel, animals, facilities, and other related issues like methods of blood sampling, anaesthesia, and euthanasia (Fig. 1). All deviations from the revised guideline from the Council of Europe's Appendix A of ETS No. 123 (2006) and the "Novo Nordisk Principles on the Use of Animals" are described and evaluated.

Furthermore, an animal welfare statement is signed by both parties to ensure compliance to the "Novo Nordisk Principles on the Use of Animals" (Table 1) and to ensure that Novo Nordisk is informed without

hesitation if any serious violations of conduct in relation to animal welfare occurs during a Novo Nordisk funded study.

We have performed animal welfare monitorings and visiting animal facilities worldwide for several years and have witnessed major changes. In general, we see much higher animal welfare standards, more and more animals are now housed in accordance with the specific needs of their species; being socially housed in bigger cages, housed under environmentally enriched conditions and socialised and trained for

future experimental procedures.

We think that the improved conditions mainly reflect an increased focus and interest among scientists and staff and a general trend within the society, but also when we perform follow-up visits, we hear and see that conditions at some external contractors have been fundamentally improved inspired by our previous dialogue and suggestions for better animal welfare.

### Acknowledgements

The great effort from all employees working with animal welfare and bioethics issues at Novo Nordisk is highly appreciated.

### References

- Council of Europe (2006) *The Revised Appendix A of the European Convention for the protection of vertebrate animals used for experimental and other scientific purposes (ETS No.123)*.
- Ottesen JL, Weber A, Gürtler H and Mikkelsen LF (2004) New Housing Conditions: Improving the Welfare of Experimental Animals, *ATLA* 32, Supplement 1, 397-404.

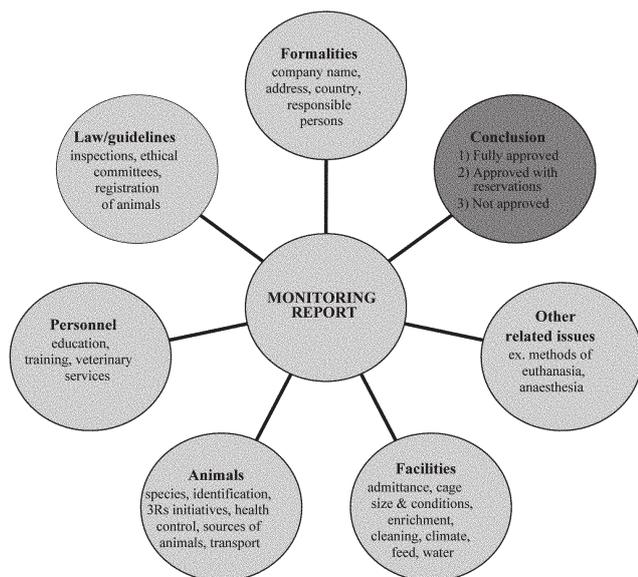


Fig. 1. The animal welfare monitoring report

Table 1: Novo Nordisk Principles on the Use of Animals

<p>Novo Nordisk considers the use of animals to be essential for the discovery, development and production of pharmaceutical and medical products.</p> <p>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.</p> <p>Animals will be used only where no available and acceptable alternatives exist.</p> <p>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:</p> <ul style="list-style-type: none"> <li>• All activities involving animals must be conducted strictly in accordance with present legislation</li> <li>• Alternatives to animal experiments must be used whenever possible</li> <li>• Transgenic animals may be used for testing and experiments when this model is justified</li> <li>• Animals bred specifically for experimental purposes must be used unless special conditions are in evidence</li> <li>• Housing, husbandry and transportation of animals must as a minimum comply with internationally approved standards <ul style="list-style-type: none"> <li>○ Housing conditions must take into consideration the special needs for the animals species in question</li> <li>○ Housing, husbandry and care of animals must be undertaken by personnel having received adequate and relevant education. The level of education must be documented</li> <li>○ Health control should be supervised by a veterinary officer experienced in regard to laboratory animals</li> <li>○ Transportation of animals must be as lenient as possible, taking into consideration the special needs for the animal species in question</li> </ul> </li> <li>• All precautions must be taken to reduce suffering and distress <ul style="list-style-type: none"> <li>○ Procedures for monitoring and evaluation of the well being of the animals as well as treatment must be implemented</li> </ul> </li> <li>• 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 in the annual Novo Nordisk Sustainability Report</li> </ul>
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