

Roche Position on Animal Testing

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As an innovative-driven global healthcare leader focused on diagnostics and pharmaceuticals, Roche aims to improve the quality of human life by providing products and services for the prevention, diagnosis and treatment of disease. Many serious diseases such as AIDS, Alzheimer's Disease, Parkinson' Disease, hepatitis, cancer, cardiovascular diseases, and diabetes, are still poorly understood and treated. Therefore, new and more effective therapies and diagnostics are desperately needed to improve the lives of patients affected with these diseases.

Roche's goal is to help alleviate the suffering caused by these and other diseases. However, this means that Roche, like all leading healthcare companies, has to undertake animal testing. The appropriate and responsible use of animals is an indispensable part of biomedical research and pharmaceutical product safety testing. Indeed, animal experiments are an integral part of understanding how basic systems of the body work, and what goes wrong with them to cause disease.

The company is well aware of public concerns about using animals in scientific procedures and takes them very seriously. Roche uses the smallest possible number of animals without putting at risk the reliability, validity, and usefulness of research and test results. In addition, the company is engaged in research to develop and validate experimental methods that can provide better alternatives to the use of animals in research. To this end, Roche also supports external institutions that aim to reduce the need for animals. However, at this time, the use of animals in basic research and in the development of drugs and technologies is required on scientific and legal grounds.

Roche is committed to act ethically and to apply the highest standards of care to animals used in scientific procedures, and conforms with international, regional and national laws and regulations, as well as with industry standards. The company uses animals appropriately and responsibly. Discomfort and unnecessary animal studies must be minimized. All employees within Roche who work with animals, as well as external contractors performing animal tests on its behalf, are strictly required to obey the law at all times, conduct their research with compassion and apply the highest standards of welfare and respect for the animals in their care. Roche is fully committed to ensuring compliance with these standards and monitors this process via internal review committees and/or animal welfare officers.

Background

1. Animal research is a necessary part of drug development

Researchers, regulators, patient groups, and members of the healthcare industry recognize that the appropriate use of animals in biomedical research and safety testing is an indispensable part of the process for acquiring the knowledge necessary to control or eliminate disease and injury in humans. In addition, regulatory bodies worldwide require efficacy and safety data for new medications based on animal experimentation before human clinical trials can be conducted. They mandate animal studies in order to reduce the risks for people and allow safer creation of new therapies. Thus, due to the lack of accepted, equivalent non-animal alternatives, eliminating the use of laboratory

animals in pharmaceutical research would significantly impede or altogether halt efforts by research-based healthcare companies to develop cures and/or more effective treatments for diseases such as cancer, AIDS, and heart disease.

Due to animal testing, the likelihood of adverse effects occurring during testing in humans can be significantly reduced. The results of animal tests enable researchers to determine which experimental compounds in advanced development are unsuitable for use in humans (~30-40%) either because the risk of potential toxicity is too great or because they do not have the desired pharmacokinetic profile, thus likely rendering them ineffective. Around 70% of serious adverse effects that occur in humans are identified at the animal testing stage. Therefore, animal testing is extremely beneficial in minimizing the risks to humans in clinical trials.

2. Valuable findings from animal testing

- Animal tests showed that Accutane/Roaccutan, a medicine to treat severely disfiguring skin diseases, is highly likely to cause birth defects. As a result, doctors are aware of the dangers in prescribing the drug to pregnant women.
- Roche has been able to discover and develop new anticancer medications (Mabthera and Herceptin, for example) that are not only much more effective but also far better tolerated than conventional cytostatic drugs.
- Roche could not have developed modern, highly effective AIDS medications with an acceptable safety profile, such as Invirase, Fortovase, Viracept and Fuzeon which allow many patients to have a better quality of life. The same applies to CellCept, the leading medication for preventing rejection reactions in patients who have received organ transplants.

3. Roche adheres to all laws and regulations

Roche complies with international rules such as those developed by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Guidelines), from the OECD, from the Council of Europe (European Convention for the protection of vertebrate animals used for experimental and other scientific purposes, ETS 123). Moreover, regional (e.g. the EU Directive on animal welfare, 86/609), national as well as local laws and regulations of countries where Roche operates are applied.

In Switzerland, at the largest research site, the applicable rules can be found in the Swiss Federal Act on Animal Protection and the Swiss Animal Protection Ordinance. In the US, where the second largest research sites are, the use of animals in laboratory research is regulated by the Animal Welfare Act through the Department of Agriculture. The use of mice and rats is regulated by the Guide for the Care and Use of Laboratory Animals as recommended by AAALAC (see below)

4. Practice and guiding principles

Locally, industry standards also govern the use of animals in laboratory research and testing. For example in the US and, more recently worldwide, the Association for the Assessment and Accreditation of Laboratory Animal Care (AAALAC) International accredits research animal care and use programs. The American Association for Laboratory Animal Science has certification programs for laboratory technicians who are

educated on the proper care and use of research animals. In addition, Roche employs in the US veterinarians who are certified by the American College of Laboratory Animal Medicine.

Within Roche, the most important research sites have already received accreditation from AAALAC, International. The Association enhances life sciences by promoting the responsible treatment of animals used in research, teaching and testing through voluntary accreditation and assessment programs. The company's sites are visited by AAALAC staff and an evaluation is made of its procedures, including animal care and use policies and responsibilities, animal environment and enrichment, housing and management, as well as veterinary medical care. The accreditation is maintained through annual reports to AAALAC as well as through visits once every 3 years. The accreditation is based on standards such as the EU Directive 86/609, the Council of Europe Convention and national legislation worldwide.

In order to ensure that animal tests conducted at Roche and by its contractors comply with laws and standards, Roche has instituted internal control processes, e.g. either through an internal Committee (in the US the Roche Institutional Animal Care and Use Committee, including two external members) or an Animal Welfare Officer (Switzerland, Germany), supported by an internal advisory body. Those control bodies/officers cooperate closely with authorities/external ethics committees. In several countries (e.g. Switzerland, Germany), animal welfare organizations are represented in such ethics committees.

5. Choice of animals for testing

The vast majority of animals used by Roche are rats and mice (e.g. over 95% in the US, over 98% in Switzerland). Very few studies use dogs, rabbits or non-human primates. A large majority of the animals used in our research and development are specifically bred for research and purchased from certified breeders.

Some human pathologies are difficult to study because they do not occur naturally in animals. Therefore, the discovery and development of new treatments and cures for many serious diseases, scientists need to involve or genetically-modified animals, i.e. transgenic and gene-targeted mice. Such animal strains mimic human diseases, thus allowing assessment of efficacy of new medicines. Moreover, the use of genetically modified mice has the potential of contributing to the further reduction in the use of 'higher' animals, such as non-human primates. Roche is committed to applying the same level of standards and ethical principles as for all other animal experimentation to genetically modified animals.

6. Reduction, Refinement and Replacement, the 3 Rs

The principle

The guiding principles of the international laboratory animal research industry are reflected by the "3 Rs": reduction, refinement, and replacement. "Reduction" involves an attempt to use fewer animals in laboratory research and the development of testing methods that require fewer animals. "Refinement" means tailoring laboratory animal procedures to minimize discomfort and to ensure proper and humane care of animal subjects. Finally, "replacement" involves the development and use of alternative research and testing methods that do not require the use of animals.

Internal measures

Roche is dedicated to following the 3 Rs for animal research and testing and to minimizing the number of animals necessary to achieve our research goals and objectives. Where the law allows and where it is scientifically possible and ethical, Roche employs medical testing procedures that do not require animals. The number of experimental animals required has already been dramatically reduced.

Roche does not use animals in biomedical research or safety-testing procedures if non-animal procedures can yield results that are equivalent to the results obtained using animal procedures. However, the variety of methods being proposed as substitutes for animal research -- mathematical models, computers and cell cultures -- are not currently capable of replacing all animal testing and regulatory bodies do not accept many non-animal tests.

Initial screening of development compounds, by means of computer modelling, extensive database searches or *in-vitro* tests (often involving human cells), is always performed. In particular, more cell culture based testing is used to eliminate acutely toxic compounds prior to animal testing. As a result, only promising compounds are tested in animals.

Around the world, Roche is supporting the development of experimental models that will also replace animal tests after the initial screening phase. One of the objectives of Roche's global Multidimensional Medicines Optimisation programme is to develop new cell-based tests that produce results that can reliably be applied to humans. In 2000 a computer program that predicts the absorption of active substances in humans without animal tests was implemented at all Roche research sites. The program utilises data on solubility and cell permeability.

Determining whether a drug is safe without the aid of animal tests is a major scientific challenge because of the complexity of the processes involved. Roche is a worldwide promoter of computerised techniques for determining pharmacokinetics and tolerability using data from cell tests and clinical studies in humans. The company invested over \$(US) 1 million. in related software applications in 2001 alone.

As an example, Roche uses isolated cells in tissue culture from animals to help determine how a developmental compound will affect an actual test subject. By using heart cells, we can begin to understand how a drug will affect the heart. As another example, using cells from the sebaceous glands of the skin, we can begin to determine the effects a test compound has on the secretion of sebum, or skin oil, in the development of dermatological compounds. As another example, we use the limulus amebocyte assay (derived from the horseshoe crab) in place of rabbits to evaluate products for the presence or absence of toxins.

When testing in animals is still inevitable, Roche is making every effort to reduce and to refine these studies. For example, Roche has invested over \$(US) 2 Mill. in a state-of-the-art laboratory for Magnetic Resonance Imaging and Spectroscopy (MRI/MRS). This modern technology allows us to analyze the living, unperturbed organism specifically for

the efficacy of drugs and for potential side effects. The method is completely non-invasive: only anesthesia is needed. Repeated measurements in the same animal lead to less variability, thus higher statistical significance is reached with fewer animals.

Roche is at the forefront of research in toxicogenomics, a technology that will enable us to use information on genetic predispositions to determine drug tolerability — with the promise of reducing the need for some animal toxicology testing.

External involvement

Finally, the company is working with other organisations to introduce techniques that will further reduce the number of animal experiments. Roche was a founding member of the Swiss 3R Foundation, whose aim is to reduce animal testing by funding research projects for new methods in line with the 3R principles of reduction, refinement and replacement, and the company continues to support the institution.