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# Animals and medicines research

## Animal research for the discovery and development of new medicines

**Countless numbers of patients worldwide have seen their quality of life improved thanks to innovative new medicines. The UK-based pharmaceutical industry is constantly researching and developing medicines which aim to improve the ways in which a range of conditions are treated.**

All new medicines must first be tested on animals to ensure that they are safe enough to be given to humans. When these tests have been shown to be successful, clinical trials will be conducted on humans. It is important to note that animals are only used in medical research when absolutely necessary and unavoidable – in situations where appropriate alternatives are not available.

The welfare of these animals is of paramount importance. Animal welfare in the UK is regulated under the Animals (Scientific Procedures) Act. The Act states that animals used in medical research should be cared for by trained, accountable staff and housed in proper facilities. In addition, the benefits of the research should justify any possible distress to the animal, and alternatives should be used wherever possible.

The majority of the UK public supports the use of animals in medical research. According to the latest MORI poll in 2014, 68 per cent of the population accept the use of animals in scientific research as long as it is for medical research purposes and there is no alternative, while a further 14 per cent are neutral.

The UK-based pharmaceutical industry is committed to developing new and innovative medicines which meet public health needs, involving the considered and compassionate use of animals where necessary.

# ABPI policy statement on the use of animals in research

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The bio-pharmaceutical industry, which the ABPI represents, has extensive research and development programmes which make a valuable contribution to people's health, and also to the UK economy. The industry has been responsible for the development of the large majority of the medicines in the world. Without vital research using animals there are many serious diseases which could not be effectively treated or managed the way they are today.

**Our industry's research using animals plays a small but essential role in the design and development of new medicines.** Research using animals is currently essential to bridge the gap between the theories developed in the test tube, and the reality of introducing a safe and effective new treatment to patients.

**Our industry only uses animals when it is necessary and when appropriate alternatives are not available.** The sector is strongly committed to the 3Rs principles of animal research (replacement, reduction and refinement), and is driving collaborative initiatives at a UK, European and international level to seek and validate replacement, reduction and refinement options.

**Our industry takes its responsibility for the animals in our care extremely seriously.** Our members maintain very high standards of animal welfare, complying with strict UK regulations and often going above and beyond these regulations. The care and use of animals is overseen by highly-skilled and professional individuals, including animal technicians, vets, and scientists, ensuring that the animals used in research are well looked after throughout their lifetimes.

**The ABPI's commitments:**

- We have signed the Concordat on openness in animal research in the UK, alongside many of our member companies, and are actively working to meet the four commitments outlined in the Concordat.
- We are committed to our ongoing collaboration with the UK's National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs), and work closely with them on an active programme to support the 3Rs in research and embed them in daily practice.
- We undertake a regular internal communications programme to ensure all our staff understand how animals are used in research and how this impacts their own role.
- We speak on behalf of our members about the use of animals in research to demonstrate and promote to an external audience our industry's values to be open, transparent and accountable for the research that we conduct, fund and support.
- We facilitate the 'non-clinical and biological discovery expert network' which consists of member companies working in the area of animal research. Their remit is to sustain and enhance the UK and European environment for non-clinical pharmaceutical research to develop new medicines, and to spread best practice, including in the area of animal research. We collaborate with others in academia, government-funded organisations and charities to achieve these objectives.

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# Research for the benefit of patients

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**Medicines have been developed for many diseases, but many others still have no long term cure. Also, many existing treatments work better for some patients than others, and some have negative side effects. Hence there is a continuing need to develop new and better medicines.**

**Research using animals plays a small but important role in the development of new treatments for debilitating diseases which will affect many of us and our family members during our lifetimes. Developing new drugs is a complex process, taking 10-15 years on average, only a small proportion of which involves animal research.**

## Time to *flourish*

Inside innovation: the medicine development process

The pharmaceutical industry develops 90% of medicines[1]

Re-investing profits from medicines enables companies to develop new medicines for patients

| | Pre discovery | Drug discovery | Pre-clinical testing | Phase 1 clinical trial | Phase 2 clinical trial | Phase 3 clinical trial | Licensing approval | Medicine available for patients |
|---|---|---|---|---|---|---|---|---|
| Average number of years taken to develop successful medicine[2] | | 4.5 years | 5.5 years | 7.0 years | 8.5 years | 11.0 years | 12.5 years | |
| Average cost to research and develop successful medicine[3] | | £436 million | £533 million | £710 million | £916 million | £1.1 billion | £1.15 billion | |
| Number of medicinal candidates tested to achieve one approved medicine[4] | | 5,000 - 10,000 candidates | 10-20 candidates | 5-10 candidates | 2-5 candidates | 1-2 candidates | 1 medicine | |
| | Based on their disease focus, companies' scientists work to understand the disease | Researchers select a 'target', such as a gene or protein, then search for a molecule, or compound, that may act on the 'target' to alter the disease | Early safety and efficacy tests are undertaken in computational models, cells and in animals | The candidate medicine is tested in people for the first time. Studies are conducted with about 20 to 100 healthy volunteers | Researchers evaluate the candidate medicine's efficacy in about 100 to 500 patients with the disease | Researchers study the candidate medicine in about 1,000 to 5,000 patients to generate data about safety, efficacy and the overall benefit-risk relationship of the medicine | Information and results from all the studies is compiled and submitted to the regulatory agencies | The medicine is now licensed for use and patients may benefit from it, subject to value and cost-effectiveness assessments and local health budget availability |

[1] IFPMA analysis of the WHO Model Essential Medicines List (2006)
[2] Paul S et al How to improve R&D productivity: the pharmaceutical industry's grand challenge, Nature Reviews Drug Discovery, Volume 9 March 2010
[3] *(in 2010 prices based on Bank of England exchange rate)*
[4] Paul S et al How to improve R&D productivity: the pharmaceutical industry's grand challenge, Nature Reviews Drug Discovery, Volume 9 March 2010
[4] PhRMA analysis, updated for data per Tufts Center for the Study of Drug Development (CSDD) database (1995)

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## Cancer

Cancer encompasses a large number of devastating diseases with a high prevalence; in the UK more than one in three people will be diagnosed with cancer during their lifetime. Many successful cancer therapies have been developed, and cancer survival rates have doubled in the last 40 years, but for many people current medicines are still not effective, or can cause debilitating side effects.

Many pharmaceutical companies are working to develop novel treatments for cancer based on monoclonal antibodies (mAb). All cells display signals on their membrane which allow them to be identified. The signals displayed by cancer cells are often different to those on healthy cells. mAb can be designed to recognise cancer cell signals and bind to them. This can then attract the person's immune system to destroy the cell, or the mAb can be joined to a toxic drug which destroys the cell when the mAb binds to it.

Such novel treatments are often first tested in mice. Cancer cell lines can be transplanted into the mice to develop a small tumour. The mice are then given the new medicine and the rate at which the tumour shrinks for example, can be used as a measure of how effective the medicine may be. The safety of such medicines is also tested in animals before they are given to humans. This is a legal requirement, to protect human volunteers and patients.

Some of these medicines are already saving lives, and many more are likely to be developed in the coming years.

## Alzheimer's disease

Over 800,000 people currently live with dementia in the UK, and as we live longer these numbers are predicted to increase greatly. Dementia and Alzheimer's disease are not only devastating for the individuals and families affected, but also cost the UK over £20 billion per year. There is currently no cure for Alzheimer's disease, and current treatments are not effective in all patients and only temporarily improve symptoms.

Genetically modified mice are playing a significant role in helping researchers understand this disease, and design new treatments. Scientists think that the damage to the brain in Alzheimer's disease is caused by the accumulation or aggregation of protein called beta amyloid. Mice can be genetically modified so that their brains contain high levels of this protein. This allows scientists to study how the protein affects the brain, and design drugs to intervene in the process.

Alongside this, scientists have been developing cell models of amyloid protein accumulation. These cell models can be used to screen for potential medicines which disrupt the accumulation of beta amyloid. However, cell models cannot tell scientists what happens in the context of the whole brain, how potential medicines will work in a whole animal, or predict side effects that the medicine may have on other systems. Therefore research using animals still has a crucial role to play in developing new treatments. This is an example of how in vitro and in vivo techniques are used alongside one another to develop new medicines.

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# The 3Rs and alternatives to the use of animals

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## THE '3Rs'

**REPLACE** the use of animals wherever possible

**REDUCE** the number of animals needed to a minimum

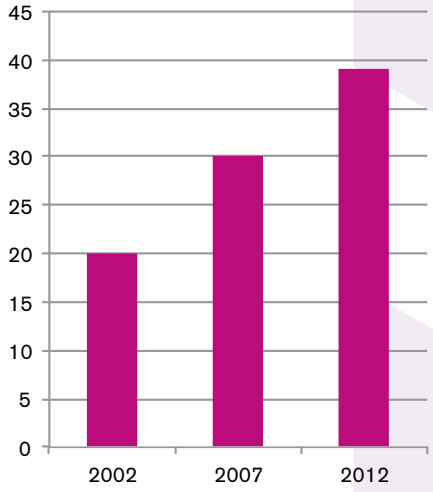
**REFINE** tests to cause animals the least possible distress

The pharmaceutical industry is actively committed to the 3Rs principles, which are accepted as the basic principles for reducing the use of animals in research and for good laboratory animal welfare. These principles are enshrined in the UK and EU laws governing the use of animals in research, so pharmaceutical companies must and do use alternative methods wherever possible – this is assessed in ethical review before permission for the research is granted. To do otherwise would be unethical and expensive.

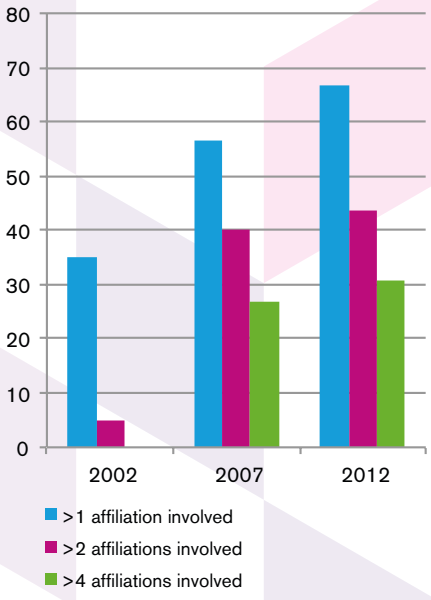
The pharmaceutical industry is always looking for new ways to replace, reduce, and refine their use of animals. However, this is not as simple as it may sound, and often requires significant research investment. An analysis of published literature supported by the ABPI (Cunningham et al. 2015 *Toxicol. Res.*, in press) found that the number of scientific papers with a 3Rs objective published by the pharmaceutical industry increased significantly between 2002 and 2012 - see graphs below. This demonstrates that the industry is taking its commitment to the 3Rs seriously, and is increasingly investing resources in research to drive forward the reduction, replacement and refinement of animal research.

Developing and validating alternatives to using animals is a scientifically challenging process, and often depends upon a larger body of R&D. The pharmaceutical industry recognises the need to work in partnership with academic institutions and small and medium sized enterprises to share ideas, expertise, funding and findings to reduce, replace and refine animal use. Between 2002 and 2012 there was a large increase in the number of 3Rs studies published with multiple affiliations, and with authors from both industry and academia. Additionally there was a substantial increase in studies with authors from contract research organisations (CROs). These data show that the whole bioscience sector, including the pharmaceutical industry, is increasingly working collaboratively towards 3Rs goals.

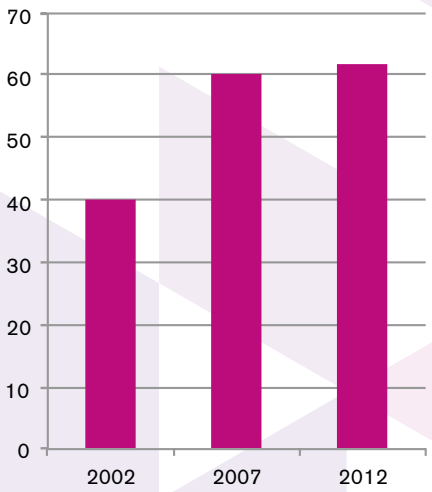
**Number of 3Rs papers with industry involvement**




**Percentage of 3Rs papers with involvement of multiple institutions**




**Percentage of industry 3Rs papers involving industry-non-industry collaboration**




Modified from Cunningham et al (2015) Quantifying the pharmaceutical industry's contribution to published 3Rs research 2002-201, Advance article, Toxicol. Res. - Reproduced by permission of the Royal Society of Chemistry

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# The 3Rs and alternatives to the use of animals

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Statistics collected by the Home Office show that the number of procedures carried out on animals by commercial organisations is 15-20% lower than it was 20 years ago, yet the number of new medicines under development in the UK remains steady, further demonstrating the industry's commitment to the 3Rs.

There is every reason to hope that these trends will continue. For example, there are a number of ongoing projects supported by the jointly industry-EU funded Innovative Medicines Initiative (IMI) which are likely to have implications for animal research, working on topics from computer modelling, to stem cells. The industry also contributes funding to, and works closely with, the UK's National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs) on an active programme to support the 3Rs in research, whilst in Europe industry participates in the Commission's European Partnership for Alternative Approaches to Animal Testing.

As our biological, medical and technological knowledge grows, we look forward to a time where animal research may not be necessary. However, currently, the complexity of human and animal life means that there are always things we need to know whilst developing new medicines that computers and in vitro methods cannot yet tell us. Our priority remains to develop safe and effective medicines, involving the considered and compassionate use of animals when necessary.

For further information visit www.nc3rs.org.uk

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# Advances in the 3Rs

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Those who work with animals in the pharmaceutical industry are always looking for new ways to reduce, replace and refine their use of animals. Some parts of the research process, which in the past required the use of many animals, now need fewer, thanks to 3Rs research and broader scientific advances. Many more processes have been significantly refined, reducing the pain and distress caused to the animals involved.

Recent examples of advances in the 3Rs made in industry include:

- **Microsampling** – To investigate how new medicines are absorbed and cleared from the body, scientists take blood samples from animals treated with the drug and measure chemical levels in the blood. Traditionally many animals were used for these tests, in order not to take too much blood from a single animal. However, advances in biotechnology and chemical analysis mean it is now possible to make chemical measurements from blood samples as small as 20µl. Taking smaller samples both reduces the negative impact on individual animals, and allows more measurements to be made from a single animal, reducing the number of animals used. Microsampling has been taken up rapidly by the pharmaceutical industry in recent years, and is now used in most companies.
- **Group housing during telemetry studies** – Before they can be given to humans, new medicines must be tested for any cardiovascular side effects. This is usually assessed in dogs. In these experiments the dogs' heart rate, blood pressure and electrical heart activity are measured using an implanted monitor, which sends the data wirelessly to a computer. Dogs are often housed individually for these experiments so the radio signals from different animals do not interfere with each other. However, it is now possible for data from different animals to be sent along different radio frequencies, preventing interference. This means that dogs can be housed together in social groups throughout the experiment, which is better for animal welfare.
- **Better anaesthesia** – Zebrafish are commonly used in drug development. For some experiments the fish need to be anaesthetised to minimise pain and distress. This is done by flowing anaesthetic into the water in the fish tank. However, some chemicals can be detected by fish. A study from one company discovered that zebrafish found some anaesthetics unpleasant, but not others. Throughout their company they now only use anaesthetics which are not aversive to the fish.

**Using statistics for the 3Rs**

Animal studies must be well designed and conducted so they produce data that is relevant, reproducible, and gives scientists confidence for decision making. Ultimately, robust studies lead to the minimum number of animals being used in research.

One company has developed an 'Assay Capability Tool' to guide the design and use of animal assays in drug development. The tool questions whether the assay answers the specific objectives of the study, whether variability in the assay has been minimised and accounted for in the study design, and whether the assay is being conducted objectively (e.g. with appropriate randomisation or blinding).

Another company has rolled out a standard requirement for good statistical reporting across all their animal studies, involving expert statisticians in the design, analysis and interpretation of preclinical research in a systematic way.

Ensuring that experiments are well designed in these ways will produce more robust preclinical data, leading to more efficient drug development and a reduction in the number of animals used to produce each medicine.

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# 3Rs Research in progress

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The pharmaceutical industry is working in collaboration with academia and SMEs on many projects aimed at reducing or replacing the use of animals, and improving drug development. Examples of such research include:

- **Induced Pluripotent Stem (iPS) cells** – It is now possible to make human heart or liver cells from iPS cells. These cells are being explored as a new high-throughput way to test the side effects of medicines on human cells, and may be able to reduce or replace some animal tests in the future. For example human heart cells made from iPS cells have recently been shown by one company to be as predictive for testing the effects of drugs on contractility as animal cells.
- **Tumour slices** – New cancer medicines are usually tested on cancer cell lines in culture and in tumour models in animals. Both these techniques have limitations. Current research is exploring tumour slices as a new model for testing anti-cancer drugs. These may be a more realistic model than cell culture, as they are 3D and contain a greater variety of cell types, as found in real tumours. These slices have the potential to reduce or replace some animal tests in the future.

**Recognising achievements**

Many companies regularly give 3Rs awards to recognise employees who have made significant contributions to the 3Rs, whether scientists, animal technicians, vets or statisticians. This is a very public demonstration of the commitment of companies to the 3Rs at the highest level, and the value they place on such work.

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# How is animal research regulated?

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### Regulation of animal research

Research on animals plays a critical role in the development of new medicines. Current European and UK guidelines recommend animal studies to be undertaken to evaluate the safety, quality and efficacy of new medicines before they can be given to humans. However, the use of animals in research is strictly regulated and animal welfare is a top priority. The UK based pharmaceutical industry has a well deserved reputation for achieving high standards of laboratory animal welfare, and works hard to maintain this.

### Regulation for patient safety

Detailed guidelines drawn up by the European Medicines Agency's (EMA) scientific committees and the International Conference of Harmonisation (ICH), as well The World Medical Associations Ethical Principles for Medical Research Involving Human Subjects (the Helsinki Declaration), detail that new medicines should be tested on animals before they can be given to human volunteers or patients. Current regulatory guidelines recommend that tests are carried out in at least two species: one rodent and one non-rodent species.

The British pharmaceutical industry plays a major role in international discussions between the American, EU and Japanese pharmaceutical industry, and their respective regulatory authorities, to ensure that tests expected by governments around the world are consistent, avoiding duplication of animal research.

The pharmaceutical industry also works with regulators to implement the 3Rs principles. For example, a cross-industry data sharing initiative driven by the National Centre for the 3Rs (NC3Rs) led to the removal of the requirement for single dose acute toxicity testing from international guidelines in 2009. The data sharing study showed that this type of toxicity test did not provide useful information above that obtained through other required studies. This change in regulatory guidelines has significantly reduced animal use and improved welfare in toxicity testing.

### Regulation of animal use

The use of animals in science is tightly regulated. In the UK, animal research is governed by the UK Animals (Scientific Procedures) Act 1986, and an EU Directive, which has been transposed into the UK legislation. These laws only permit animal research if:

- the information sought cannot be obtained using non-animal methods
- the likely benefits of research justify any possible distress to the animals
- the studies are properly designed so that as few animals as possible are used
- any discomfort or suffering is kept to a minimum by appropriate use of anaesthetics or pain killers
- the staff conducting the research are fully trained and authorised
- the research facilities provide the necessary expertise and facilities to ensure animals are well cared for before, during and after procedures, including veterinary care and welfare advice

The 3Rs of animal research are written into these laws, so scientists are always looking for ways to reduce, replace and refine their use of animals (see insert: '3Rs and alternatives to the use of animals' for more information).


Image courtesy of Understanding Animal Research / Wellcome Images

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# How is animal research regulated?

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### Licensing of research using animals

The use of animals in science in the UK is regulated by the Home Office. Laboratories and research teams require three types of Home Office licence before they can work with animals. These are:

- an establishment licence, to ensure that the animal houses and laboratories provide the necessary expertise and facilities to care for the animals
- a project licence, to ensure that the likely benefits of the project outweigh any possible distress caused to the animals, that the project is properly designed, and that appropriate steps will be taken to minimise pain and distress
- a personal licence to ensure that the person carrying out procedures on animals is fully trained and competent.

### Inspection

In addition, Home Office inspectors - all qualified vets or doctors - regularly visit establishments to check that animal research is being carried out in a proper, legal and humane way. They often arrive unannounced and have to be given access to the whole establishment.

### Care and welfare

The UK law is clear - animals used in research must be treated with care and respect. All establishments have an Animal Welfare and Ethical Review Body who promote animal welfare and the 3Rs, and review animal care standards in their organisation. Many companies go above and beyond the law to ensure that animal welfare, and hence animal science, is maintained at the highest levels. For example, some companies undergo voluntary external review by the Association for the Assessment and Accreditation of Laboratory Animal Care International. Companies also work towards the 3Rs of animal research in multiple ways, from large cross-sector collaborations, to small scale refinements in practice. See insert: 'The 3Rs and alternatives to the use of animals' for more information.

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# Animal studies in the Pharmaceutical Industry

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The exact experiments carried out using animals during the research and development of new medicines depend upon both the disease being targeted and the nature of the new medicine. However, some types of study are routinely carried out by the pharmaceutical industry. Here we describe some examples of experiments carried out in the industry and their important role in the development of new medicines. We also discuss the harms the animals experience and how these are minimised.

It is important to note that before any study is started, the plans are reviewed and discussed with a local animal welfare and ethical review body, which always includes a vet and an animal care and welfare officer, as well as undergoing a harm-benefit review by the Home Office. These ethical review processes may identify additional ways the 3Rs can be applied in the studies. They can also help define the acceptable limits of pain or suffering that the animals may experience, which will be as low as possible whilst allowing the scientific questions to be answered. If these pre-defined limits are reached, studies will be terminated. See the descriptions of the following specific studies for more details.

## General toxicology tests

General toxicology studies are essential to assess the safety of potential new medicines. These tests are carried out in two species, one rodent and one non-rodent, usually a dog, minipig or primate. Using two different species increases the detection of side effects relevant to humans.

The animals are divided into groups, and each group receives a different dose of the new medicine over the course of several days, weeks or months depending on the treatment. The animals are closely monitored for any adverse effects, and blood and urine samples are collected and analysed for drug levels and other changes.

**Aim:** To assess potential side effects of new medicines before they are given to humans.

**Overall harms:** Some side effects of the medicines are likely, as this is the purpose of the study. These effects will depend on the medicine being tested. Most side effects are mild to moderate in severity, such as causing weight loss. In some animals effects may be more severe.

**What happens to the animals:**

- **Identification** – animals need to be tracked throughout the study, so may be ear notched (mostly rodents), tattooed, or have an ear tag or microchip implanted (mostly larger animals). These all require the animal to be temporarily restrained, and can cause transient pain, like being injected with a needle.
- **Dosing** – the medicine has to be administered to the animals, ideally via the same route as it will be given to humans. Most commonly, substances are given orally (via the mouth) or intravenously (IV, injected into a vein). Oral dosing usually involves a tube, or 'gavage', being inserted into the animal's stomach via their mouth. This can cause discomfort and has a small risk of damage to the animal's internal lining of the throat. IV dosing involves an injection into the vein: the animal must be restrained and the injection causes a similar level of discomfort to having a blood sample taken.
- **Blood sampling** – blood samples are taken throughout the study, to monitor levels of the drug and to relate these to possible side effects of the medicine. A needle is inserted into a vein of the animal, and a small amount of blood removed, very similar to human blood tests. Alternatively, a small tube, or 'cannula', can be inserted into the vein allowing multiple samples to be taken without repeated needle entries. This requires surgery whilst the animal is anaesthetised. In a small number of animals, there may be local pain or inflammation following surgery. There is also a low risk of infection to the wound.
- **Euthanasia** – at the end of the study the animals are humanely killed and their tissues examined macro- and microscopically for any adverse changes.

**How the principles of the 3Rs are applied:**

- *In vitro* tests – medicines are tested *in silico* (by computer modelling) and *in vitro* (on cells and tissues) before they are tested on animals. Only the most promising candidate medicines are tested on animals, reducing the number of animals needed, and drugs that can be predicted to cause severe toxicity are not tested on animals.
- Microsampling – new technology means that drug and metabolite levels can be measured from very small samples of blood. Taking smaller blood samples reduces the impact on individual animals, and means fewer animals are needed overall.

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# Animal studies in the Pharmaceutical Industry

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## Cancer medicine research and development

Potential new cancer medicines are first tested on cancer cells *in vitro*. The most promising are then tested for their potential to treat cancer in animal models.

One common model is known as a xenograft model. Animals, nearly always rats or mice, are injected under the skin with a small number of animal or human cancer cells. These multiply and divide forming a small tumour. The animals are then given the new medicine, and the effect of the medicine on the size of the tumour is measured. At the end of the study the animals are humanely killed so the effects of the medicines on the tumour can be investigated at a cellular level. Studies typically last from a few weeks to a couple of months after injection of the tumour cells.

**Aim:** To assess the potential of new cancer drugs to treat tumours.

**Overall harms:** If tumours grow too large they may affect the movement of the animal or cause some discomfort – for this reason the size of the tumour is carefully monitored and the study is ended if the tumour exceeds a certain size. Many cancer drugs can have side effects in animals, as they do in humans, such as diarrhoea or weight loss. Animals are carefully monitored for such effects, and the study will be terminated if these become too severe.

**What happens to the animals:**

- **Immunosuppression** – these studies are most often carried out in mice that have a genetic mutation which means they do not have a functioning immune system, so that they do not show an immune reaction and reject the tumour cells. This means that the mice are susceptible to infections, so are kept in specially clean and ventilated cages and carefully monitored.
- **Identification of animals** – see previous description.
- **Injection of tumour cells** – a small volume of liquid containing cancer cells is injected under the skin. This can cause mild discomfort, like a vaccination injection for humans.
- **Measurement of tumour size** – animals are held in the hand, and the size of the tumour is measured using callipers, which might cause mild discomfort.
- **Dosing** – the potential new cancer medicines are administered; see previous description.
- **Euthanasia** – at the end of the study the animals are humanely killed and the tumour tissue examined macro- and microscopically to explore the effect of the medicine.

**How the principles of the 3Rs are applied:**

- *In vitro* tests – potential new medicines are first tested *in silico* and *in vitro*, so only the most promising medicines progress to being tested on animals.
- Monitoring – animals are monitored carefully by trained staff for infection or side effects of the tumour or medicine. Limits of allowed side effects are predetermined in discussion with the animal welfare and ethical review body (see introduction), such as the maximum size of the tumour, or maximum amount of weight loss. The study is terminated if these limits are reached, limiting the pain or suffering experienced by the animal.
- Imaging – in some cases, non-invasive imaging such as MRI can be used instead of callipers to give better information on tumour size and composition over time and reducing the number of animals used.

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# Animal studies in the Pharmaceutical Industry

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## Drug metabolism and pharmacokinetics crossover design study

It is important that scientists understand how new medicines are absorbed, metabolised, distributed and excreted from the body – currently no computer or cellular model can completely replicate these processes in a living animal, so animals must be used for these studies. Animals are dosed with different drug concentrations, and blood and urine samples are taken to analyse the levels of drug and metabolites over time. These studies can be carefully designed as 'crossover studies' which allow scientists to gain the most information possible from the minimum number of animals.

**Aim:** To assess the absorption, distribution, metabolism and excretion of new medicines *in vivo*.

**Overall harms:** These studies should have few overall adverse effects on the animals as the dose levels of new medicines used are within the range that will be used as a treatment for humans.

**What happens to the animals:**

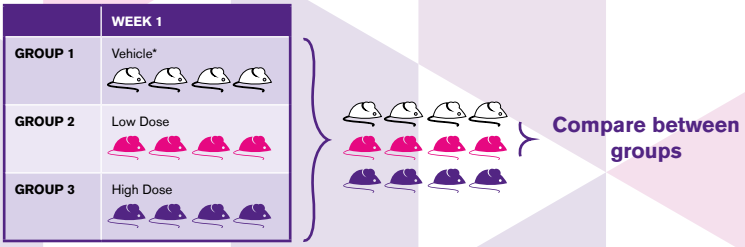
- **Identification of animals** – see previous description.
- **Dosing** – medicines are administered to the animals, as described previously.
- **Blood sampling** – see previous description.
- **Metabolism cages** – to measure levels of drugs and metabolites being removed from the body, the urine and faeces of the animals must be collected, measured and analysed. To collect these, the animals, especially rodents, often have to be kept in a special cage with a grid or slatted floor without bedding. The length of time the animals are kept in these cages varies but studies are usually completed within one week. As this is uncomfortable and stressful, animals are very closely monitored and housed in these cages for the minimum duration necessary to achieve the study's scientific objectives.
- **Euthanasia** – At the end of most studies the animals are killed humanely and the levels of drug and metabolite accumulated in different organs and tissues are investigated. Following some studies, the animals may be re-used for further experiments, reducing the total number of animals used. In a few cases, particularly where dogs have been used, the animals can be rehomed following these studies.

**How the principles of the 3Rs are applied:**

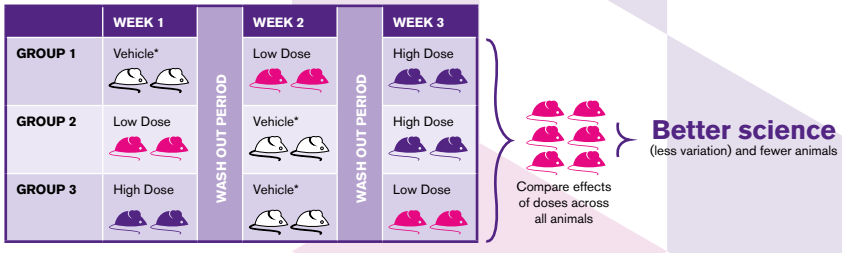
- Study design – a crossover design can be used (see diagram below), to obtain the maximum amount of data from the minimum number of animals. Care is taken, however, to limit the number of potentially stressful procedures an animal experiences in its lifetime.
- Microsampling – see previous description.
- Re-use – in the majority of these studies animals suffer very few adverse effects and are perfectly healthy at the end of the study. Therefore they can sometimes be re-used for other experiments, after their health has been assessed by a vet, if it is not necessary to use their tissues for analysis. Re-use is important, to reduce the total number of animals used. However, permission from the Home Office is required to re-use animals to ensure that individual animals do not undergo too many painful or stressful procedures in their lifetime.

### Traditional PK study design

In a traditional study each group of animals receives a single dose of the medicine, and groups are compared to each other at the end of the study. In a crossover design, each animal receives multiple doses of the drug over a period of several weeks or months. This allows multiple data sets to be collected from a single animal, and reduces variability in the data by allowing the effects of the medicine to be compared to the effects of no medicine within a single animal. This reduces the total number of animals needed in the study (see diagram to right).




### Crossover design




*Vehicle is the solution in which the drug is dissolved. It may be water or another solvent which has minimal effects on the animal. One group is given the vehicle alone, without drug, as a control group.

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# Animal studies in the Pharmaceutical Industry

Bringing medicines to *life*

## Pain model

Chronic pain, such as in arthritis in humans, is a complex process involving peripheral parts of the body such as joints, and multiple components of the nervous system. Therefore it cannot currently be completely modelled in cells or tissues. Rodent models of chronic joint pain are used to investigate underlying pain processes, identify novel targets, and test potential new medicines.

One model is to inject a chemical called monosodium iodoacetate (MIA) into the leg joint (knee) of a rodent. This causes the progressive loss of the cartilage in the joint, leading to local inflammation and pain. This model has been extensively refined to minimise the harm to the animals while generating useful data. The experiments and statistical analysis are also carefully designed to maximise the value of the data.

**Aim:** To discover potential new medicines to treat chronic pain.

**Overall harms:** As in human conditions of chronic pain, such as rheumatoid arthritis, the animal experiences joint inflammation and some pain. The dose of MIA is chosen to limit damage to the joint such that there is no observable inflammation and the animal's mobility is not impaired. Animals are closely observed for effects on mobility and signs of severe discomfort; if these are seen the study is terminated.

**What happens to the animals:**

- **Anaesthesia –** To minimise distress during the following procedures, the rodents are anaesthetised, usually using an anaesthetic gas. The animals are placed in a box and the anaesthetic is delivered until the animal is asleep. This can cause minor distress or disorientation to the animals, as it might do for humans.
- **Injection –** MIA is injected into one knee joint of the animal whilst it is anaethetised; as such this injection should not cause any suffering to the animal initially. However, over time this chemical damages the cartilage of the joint, causing increased sensitivity of the joint. By careful choice of MIA dose the animal will not experience pain such that its mobility is impaired.
- **Nerve recordings –** 14–17 days after the MIA injection measurements of joint sensitivity are carried out under general anaesthesia. Nerve recordings are taken from a single cell in the spinal column in response to rotation of the knee joint, and the effect of potential new medicines on these responses can be evaluated. Blood pressure can also be measured whilst the animal is under anaesthesia, and blood samples can be taken as described previously, to evaluate levels of the medicine.

**How the principles of the 3Rs are applied:**

- Anaesthesia – by carrying out several of the procedures under anaesthesia the distress and pain of the procedures is kept to a minimum.
- Aseptic technique – surgery is carried out in conditions known as 'aseptic technique', which means that everything in the operating room is sterile, as in human surgery, minimising the risk of post-operative infections.
- Monitoring and humane end points – the animals are monitored carefully by experienced staff on a daily basis. The level of discomfort, pain or inhibition of movement that is 'acceptable' is determined in advance (see introduction). If an animal reaches this limit, it will be euthanised to minimise its suffering.
- Experimental design – studies are planned with statisticians, treatments are randomised, and the operator is 'blinded' to the treatment, which means he or she does not know what the treatment is or if it is an inactive control. These measures ensure that the operator cannot bias the results of the study, and so improve the quality of data obtained. Maximising the value of data in this way means fewer animals are needed in total.

Image sourced from:
*Understanding Animal Research*

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RMI-0035-10/15

# Myths and reality

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**Myth – Medicines don't need to be tested on animals**

Reality –Medicines do need to be tested on animals. European and UK regulations require animal studies to be undertaken to demonstrate the safety, quality and efficacy of new medicines before they can be given to humans. The choice is a stark one: either we undertake animal research or we stop developing new medicines.

**Myth – There are lots of ways to carry out these tests without using animals**

Reality – By law, animals must not be used in research if viable non-animal techniques are available. The pharmaceutical industry is driving 3Rs collaborative initiatives at a UK, European and international level to seek validated replacement, reduction and refinement options. However, at the moment, non-animal tests – such as those using cell cultures or computers - are limited because they don't reveal the full impact of a medicine on the major organs of the body.

**Myth – Animals are nothing like humans – any information that you get from them is useless**

Reality – There are great biological similarities between humans and animals. Of course there are some differences, but these will be taken into account during any project and different species may be used to allow for variabilities. Studying how diseases and drugs affect animals can give us important clues to help us develop effective and safe medicines.

**Myth – Nobody knows what scientists get up to behind closed doors**

Reality – Animal research is strictly monitored, and in the UK we have very high standards of animal welfare to ensure animals are well looked after and humanely treated. The EU and UK law is clear - animals used in research must be treated with care and respect. Many companies go above and beyond the law to ensure that animal welfare is maintained at the highest levels, and government inspectors can – and do – make regular unannounced checks to ensure that companies follow the regulations.

**Myth – More animals are used than is necessary**

Reality – Scientists have strong ethical, economic, and legal obligations to use animals in research only when necessary. The law does not permit the use of animals where non-animal alternatives are available, and studies must be designed to use the minimum number of animals to achieve the scientific objective.

**Myth – Animal research is cheap so pharmaceutical companies use it to make bigger profits**

Reality – Animal testing is neither cheap nor easy. It is much more expensive than many non-animal methods, in part due to the number of staff required to look after the animals' welfare. It is also important to bear in mind that it typically takes 10-15 years and costs approximately £1.15 billion to make one new medicine available to patients.

**Myth – Animal research gives misleading information, making medicines looks safe when they are not**

Reality – No one expects animal research to tell researchers everything, but they do provide a good starting point. Animal research can indicate what reactions to expect in patients, allowing appropriate monitoring. It also provides information on likely safety thresholds, ensuring that human studies can be conducted safely and with less risk of adverse events. It takes years to build up a clear picture of how a medicine works and behaves – animal research represents just one piece in the jigsaw.

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# Specially protected species

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Some species are afforded special protection in the UK under the law which regulates the use of animals in research. These species are cats, dogs, non-human primates and equidae (horses and donkeys). It is not permitted to use these animals in research if any other species are suitable for the purposes of the research, and available for use.

Over 90% animals used in research in the UK in 2013 were rats, mice and fish.

In some areas of research the use of specially protected species is judged to be justified, as they provide important information that could not be obtained using other species. Studies in these species typically use much lower numbers of animals and accounted for just 0.4% of animal procedures in 2013, with non-human primates making up just 0.08%.

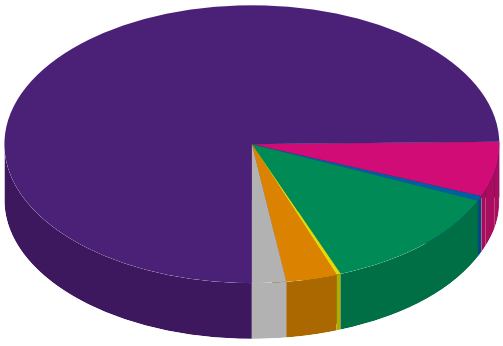
The use of great apes is already forbidden in Europe, with special provision for public health need (e.g. emerging pandemics). No great apes have been used in Europe for experimental purposes since 1999.

For the development of new medicines in the pharmaceutical industry, the most commonly used specially protected species are dogs and non-human primates.

## Dogs in the development of new medicines

Current regulatory guidelines for testing new medicines recommend that tests are carried out in at least two species: one rodent and one non-rodent species.

Dogs are often used as the second species in safety testing of new medicines. Using dogs in addition to rodents increases the detection of adverse drug events. Therefore these tests provide important information which can prevent potentially dangerous drugs being given to humans, or inform monitoring and dosage in human trials.



| | % |
|---|---|
| Mice | 74.73 |
| Rats | 6.46 |
| Other rodents | 0.69 |
| Fish | 12.31 |
| Reptiles/amphibians | 0.27 |
| Birds | 3.41 |
| Non-human primates | 0.08 |
| Other mammals | 2.05 |

Total approx. 4.12million procedures in 2013.
This figure includes breeding to produce genetically modified animals (total 2.1million).

*Annual Statistics of Scientific Procedures on Living Animals Great Britain 2013, UK Home Office*

## Non-human primates in the development of new medicines

The use of non-human primates in research rightly merits special consideration because of their highly developed cognitive abilities and the inherent difficulties in meeting their complex social, behavioural and psychological needs in a laboratory environment. Applications for the use of primates are carefully scrutinised by the Home Office on a case by case basis, with additional advice from an independent committee, and their use is only allowed when no other species is suitable.

In 2007, following a major independent UK review led by Sir David Weatherall, leading scientists reported that there is a moral and scientific case for the carefully justified use of non-human primates in research – provided it is of a high quality and has the potential to benefit mankind, and if it is the only way of solving important scientific or medical questions.

Non-human primates are used to evaluate the efficacy and safety of certain medicines and vaccines, which are unlikely to act in the same way in other species, to meet the requirements of worldwide regulatory authorities and ensure human safety. Non-human primates are also used in limited areas of biomedical research including some research into the following debilitating diseases: infectious diseases (HIV, malaria, TB, hepatitis); neurodegenerative disorders (Parkinson's, Alzheimer's); mental disorders (schizophrenia, depression); and immune-based diseases (diabetes, multiple sclerosis).

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The National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs) works in partnership with the pharmaceutical industry to review the use of primates in drug development, with the aim of minimising their use and enhancing the implementation of the 3Rs. For example, non-human primates are often used to investigate whether new medicines which target the central nervous system have a high potential for abuse, i.e. whether the medicine may be addictive. However, recent NC3Rs work[1] has demonstrated that addiction tests in rodents show good similarity with humans. This should lead to a reduction in the use of non-human primates for this test in future years.

Banning the use of non-human primates in Europe would not remove the requirement for research using these animals. It would simply mean that the research would be conducted outside Europe, where the standards of animal care and use may be much lower.

The use of non-human primates in research does not pose any threat to conservation. None of the species commonly used in research are listed as endangered by the Convention of International Trade in Endangered Species, and most research animals are purpose-bred. In addition, the industry supports the development of self-sustainable colonies of non-human primates.

1. Working with the pharmaceutical industry, NC3Rs, 2014

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**Further information**

www.understandinganimalresearch.org.uk
(Understanding Animal Research)

www.amrc.org.uk
(Association of Medical Research Charities, AMRC)

www.efpia.eu/about-medicines/development-of-medicines/animal-use-and-welfare/
(European Federation of Pharmaceutical Industries and Associations, EFPIA)

www.animalresearch.info/en/
(AnimalResearch.info – the contribution of animal research to medical science)

www.animaltestingperspectives.org
(Animal testing and research dialogue)

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