



European Federation of Pharmaceutical Industries and Associations

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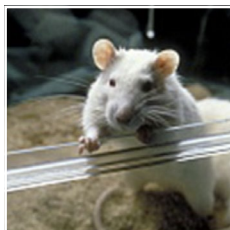
Enforcing

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Putting animal welfare principles and 3Rs into action



European Pharmaceutical Industry
2015 Update



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This report actually offers you the best of both worlds as it produced in an interactive PDF format which can be used just like any normal PDF, and it is therefore easy to print and read like a brochure; but if you are using it online or on a tablet, you can use the interactive features just like a website.

When you are using it in this format you can:

- * Click on the header buttons (Beyond Compliance; Leading by Example; Open Communications) allows you to jump to a new section
- * Click the previous and next button enable you to navigate within each section
- * Some pages contain hyperlinks



Hyperlinks are **coloured text** within the body text.



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The use of animals in research is a complex and emotive subject. The pharmaceutical industry firmly believes that in order to advance medical science for the benefit of patients and society as a whole, yet in many cases it is today impossible to dispense with animal subjects altogether.

Bear in mind that, despite the fact that we have made impressive progress in a number of key areas, including oncology and diabetes, there remain significant challenges across a range of chronic disease areas. These include chronic diseases such as cancer, diabetes, disorders of the central nervous system (dementia, Parkinson's and schizophrenia), rare diseases, infectious diseases (HIV and hepatitis) and diseases affecting people primarily in developing countries.

For the industry, the task is to develop appropriate new therapies and diagnostics that can be translated from a proven laboratory-based concept into a product that works in humans. A significant emphasis, though, must also be placed on promoting

patient safety and in many cases this cannot be done effectively without involving animals in the testing process.

The pharmaceutical industry stresses that, as a responsible sector, we are utterly committed to the key principles of the 3Rs (Reducing the number of animals used, Refining experiments to minimise the impact on animals, and Replacing animal experiments wherever possible with alternatives), and through them, to ensuring high standards of animal welfare in the research process. Therefore, we only use animals: where absolutely necessary; in minimum numbers to achieve the scientific objective; and while ensuring that they suffer the minimum pain and distress (3Rs).

This triple concept, though developed some 50 years ago, continues to be refined and improved upon. The ongoing aim is to improve the quality of life for both people and animals by developing new products and services for the diagnosis and treatment of diseases.

With this in mind, the examples included in this report seek to outline firstly the need for

controlled and limited animal testing for the advancement of science for the benefit of patients. Secondly, they serve to underline the evolution of science and technology, which changes the biomedical research paradigm. Thirdly, they illustrate efforts made by the pharmaceutical industry to adhere to the 3Rs principles of reducing, refining and replacing animal tests and developing a culture of care.

Previous reports "Putting Animal Welfare and 3Rs into Action" are available at:



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- * How do scientific advances help processing 3Rs and Welfare?
- * What internal and external industry initiatives facilitate the implementation of staff training programmes in animal welfare and care?

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- * How do we share and encourage good practices, based on 3Rs principles across the pharmaceutical industry?
- * How do we stimulate the implementation of global animal welfare standards?
- * What is being done to implement rapidly and enforce across Europe the revised European Directive 2010/63/EC on the protection of animals used for scientific purposes?

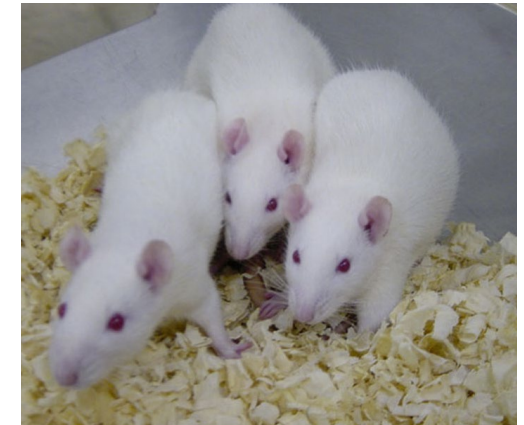
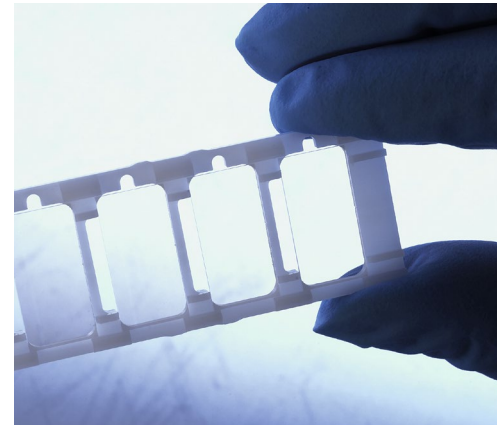
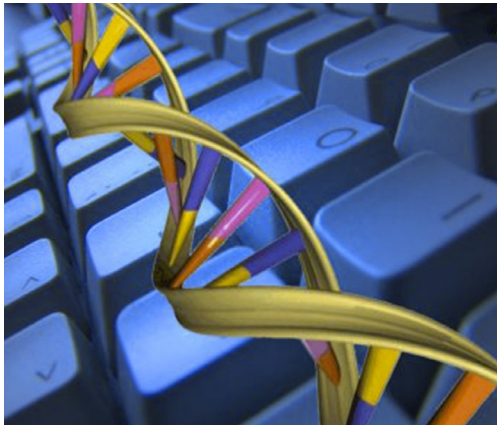
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Committing to Open Communication

- * How do we contribute to an open and constructive dialogue on animal welfare?
- * How is industry communicating the progress made in animal welfare activities, specifically the 3Rs?



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Question: How do scientific advances help processing the 3Rs and Welfare?

In Silico ADME screening to ensure that only compounds with the most favourable metabolic profile move into animal testing

In silico Absorption/Distribution/Metabolism/Excretion (ADME) is a set of computer-based tools that help to select only the very best compounds to advance into animal models. Prior to in silico ADME, animal tests were required on a vastly larger set of compounds. Screening compound structure before synthesis, increases the effective number of compounds that can be evaluated, often exponentially, without any additional animal testing. Only the best compounds are finally selected for animal studies and teams can advance projects faster without increasing animal use. In silico ADME supports our goals of advancing quality medicines while promoting the ethical use of animals.

Zebrafish screening for reproductive and gastro-intestinal safety and convulsion potential

Zebrafish fertility, small size, and transparency make them suitable for evaluating

developmental toxicity, safety assessment of cardiac, visual, and gastrointestinal (GI) functions. GI intolerance is a common preclinical finding and a potentially serious safety concern in clinical development. A zebrafish assay, developed to observe GI functions that convincingly could predict effects in humans, continues to contribute to reduction of animal use later in development. A zebrafish assay has also been validated for evaluating the potential of new drugs to cause convulsion/seizure. Routinely implemented as a screening test during the drug discovery process, it replaces an in vivo rat study. This change saves some 200 rats/year.

Cell-based tests to measure toxicity

A project team developed methods to isolate individual cell types from the pancreas of rats for assessing pancreatic toxicity. This has reduced animal use by over 95% and improved the team's ability to identify the best compounds. The team is now successfully applying the techniques to other cell types.



VFA

Refinement of mouse model skin transplantation

While improving the welfare of animals studied, a team developed and optimised a mouse model of a skin graft model to study bandaging, anaesthesia and male/female usage. The original bandaging procedure was improved by using flexible tapes and plastic tube bandages with smoothed edges to cover the tape. This helped reduce the risk of friction that could irritate the skin graft. Inhaled anaesthesia replaced

injectable anaesthetics, so that mice recovered as soon as the anaesthetic mask was removed. By using less aggressive female mice and better understanding signs of distress to adapt painkiller usage, both the quality of science and welfare have been improved.

Development of therapeutic antibodies using mouse models

The development of therapeutic proteins or antibodies targeting auto-immune or

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inflammatory disorders requires the use of humanised mouse models* to evaluate their potency and efficacy. These models represent powerful tools for studying the formation and development of blood cells, inflammatory diseases and viral host-pathogen interactions. They are helping to accelerate the development of novel therapies in immunology diseases and oncology. Historically, the data of these multi-source models have been subject to significant variability. Development of a new, refined, humanised and standardised mouse model has led to a reduction in the number of animals used by 50%.

*“Humanised mouse” are mouse carrying functioning human genes, cells, tissues, and/or organs

Modifying the screening sequence for Identification of cardiovascular adverse events

The identification of cardiovascular adverse events is critical for progressing new therapies. By changing the screening sequence of screening tests to obtain early in vitro data (i.e. using cell and tissue cultures) that is

highly predictive of the adverse events that are observed in the clinic, the need for testing compounds in animals has been significantly reduced. The Langendorff-perfused isolated heart yields data on electrocardiography, potentially replacing in vivo anaesthetised guinea-pig and rat studies. In guinea pig isolated heart studies, only 4 animals are needed for in vitro study versus typically using 12 animals anaesthetised animals for (a 67% reduction in animal usage.) In addition, in vivo studies of the movement of the drug into, through, and out of the body (pharmacokinetics) are not required ahead of testing the compounds, saving further animals. Sharing tissues whenever possible has with other in vitro assays has led to further reductions.

Tissue-based assays in place of in vivo

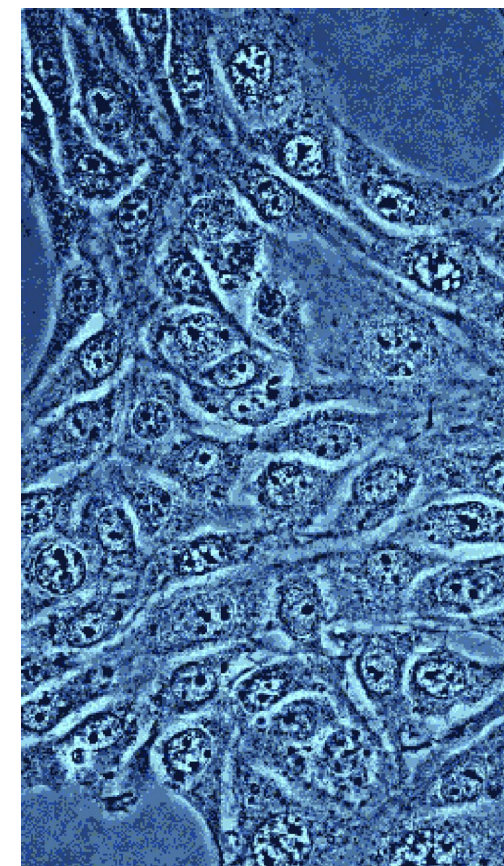
Unwanted effects on blood pressure (raised or lowered) can limit the usefulness of new medicines and stop their development. A safety team has developed a rat aortic (from the main artery in the body) tissue-based assay that replaces whole animal studies. Relaxation or contraction of the aortic muscle provides a

direct measure of compound effects and the in vitro preparation allows the team to apply sophisticated genetic techniques to understand how unwanted effects arise. In this way the team has reduced animals use by approximately 90%.

Novel approach for the reduction and refinement of animal use in experimental modes of protein synergy

The combined effect of certain proteins can reinforce immune response. Therapeutics that can simultaneously target these proteins may therefore be more effective than single-target therapies in specific diseases. Studying these complex effects is very difficult and might require large numbers of animals.

A novel approach has been developed for the refinement and reduction of animal use in developing experimental models of protein synergy: by applying refined study designs and statistical analyses, both the number and size of study groups were reduced, thereby cutting the total number of animals by almost 60%.



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Vaccine consistency approach

For certain vaccines, regulators require each batch to be tested in animals to ensure its quality. For many years, scientists worked on approaches that exploit new in vitro process release methods during the manufacturing of vaccines, which could ultimately replace current testing methods. To demonstrate that this approach would work (proof of concept), animal and human health sectors joined forces and developed a project proposal that will be implemented within the framework of a public/private consortium within the Innovative Medicines Initiative programme.

Efficacy of novel vaccines

In order to determine the efficacy of a novel vaccine against multiple strains of an infective organism, an in vitro blood serum assay was developed to replace extensive animal work. By analysing the toxin proteins responsible for disease development, it was possible to assign similar strains to a number of groups. In combination with a better study design, the number of hamsters used in studies supporting this vaccine project was cut by about 100-200

in total. In vivo work has not been eliminated, but significantly reduced. The approach may be applicable to other novel vaccines and infective agents.

Potency testing for hepatitis B vaccine

A potency test for hepatitis B was undertaken in rodents. A new ELISA test (full in vitro method) has been successfully developed and validated to replace animal testing. Proposed changes to quality control have been submitted to the competent authorities for acceptance.

This replacement test has been granted the LEEM CSR awards, category 'Coup de Coeur':

<http://bit.ly/1E5Yb68>

Model to assess efficacy of pain treatments

One model for assessing the efficacy of pain treatments involves the collection of data from single neurons in the spinal cord of deeply anaesthetised rats. Significant refinements to the experimental design of these studies have resulted in higher quality data, using fewer animals. A statistical power analysis and sample size calculation ensured that variations in the



assay were understood and that the appropriate number of animals was used. In addition, the use of Dried Blood Spot* samples from earlier studies replaced the larger plasma samples normally taken and improved the health of animals by reducing blood loss during experiments. Over the course of a year, the number of animals can be reduced by approximately 23%.

* a form of biosampling where blood samples are blotted and dried on filter paper; this technique allows to limit the sample to only a few drops of blood.

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Question: What internal and external industry initiatives facilitate the implementation of staff training programmes in animal welfare and care?

Refined methods for blood collection

Sharing implemented, refined methods for blood collection and vein catheter procedures with external parties (both industry partners and academia) by practice. These methods are furthermore explained at conferences around the world.

Training of animal carers

A programme has been initiated in some companies ensuring the transfer of staff working with animals (vets, lab techs, care takers) between global sites to ensure global standards.

Training for staff responsible for planning and statistics

An internal Ethical Review Council offers training on planning and the statistical

analyses of animal experiments to scientists and responsible personnel involved in studies.

Severity grading

An internal expert group has been established to guide scientists on severity grading - i.e. assessing the level of distress and suffering for the animal. The group has collected internal examples to share and train personnel in grading. Members of this group share knowledge with industry partners and academia.



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Question: How do we share and encourage good practices, based on 3Rs principles, across the pharmaceutical industry?

The use of 3-D hepatocyte screening for liver safety

3D cultures are constantly being refined and applied to characterise the potential of new drug candidates to induce liver toxicity. 3D liver cell systems provide a novel means to conduct studies on drug candidates to predict or characterise human-specific liver toxicity. A pharmaceutical company is a member of a consortium whose primary objective is to characterize some of these methodologies.

3Rs Award

In 2009, Novo Nordisk set up an internal 3Rs Award, to honour employees who improve the conditions for animals used in research, and to emphasise the importance of a constant focus on animal welfare. Novo Nordisk employees participate globally in this award process. The initiatives are available on the company homepage:

Building of a new pig vaccine R&D facility

An open and constructive dialogue with experts

in pig research academia and the committee for animal welfare conformity of the Germany Agricultural Society led to the planning, design and building of a new pig vaccine research & development facility in Germany, to implement best practices standards. The facility is one of the few research facilities in pig vaccine R&D in Germany. The proactive integration of external experts into the planning approach allowed for the integration of the most recent state-of-the-art opinion on pig husbandry. At the same time, it permitted critical scrutiny of new concepts and their successful, operational implementation in the pig husbandry practice.

Supporting 3Rs centres

Industry continues to support a number of 3Rs centres, including the newly-established centre by the Danish Ministry of Food and Agriculture, which will provide Euros 200,000 of grants every year to 3Rs initiatives.



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Question: How do we stimulate the implementation of global animal welfare standards?



Global standards

A programme has been initiated promoting the transfer of staff working with animals (vets, lab techs, care takers) between global sites to ensure global standards.

- To ensure global standards, a global laboratory animal science manager group has been established. This group meets a minimum of 4 times per year and shares performance goals.
- A governance structure has been implemented ensuring ethical alignment by local animal care and use committees (IACUCs) reporting to the company Ethical Review Committee.

Animal facility planning processes

In Germany, new animal facility planning processes take into consideration the best practice principle in animal welfare. Regulatory standards across the world still vary. For a German pharmaceutical company, European planning standards continue to be the core element and reference point for facility planning. This is also the case in regions with lower legal standards (e.g. China). The planning of new facilities is assessed via so-called “peer reviews”, including company representatives for animal welfare, during the planning, design and implementation process.

Global Cooperation in animal health guidelines

Some legal EU regulations and VICH guidelines that can reduce animal consumption in the context of vaccine release testing are not automatically acknowledged in all countries worldwide. Pharmaceutical companies are organising meetings with local authorities for example in Mexico, to discuss European requirements.

Participation in international collaborative studies

Authorities involved in cellular Pertussis vaccines have set up an international working group to evaluate the replacement of a histamine sensitisation test in mice required to assess residual toxicity. Vaccine companies are actively involved in assessing alternative methods. An international collaborative study is currently underway, with first results expected in 2014.

Sharing 3Rs initiatives worldwide

Companies continue to participate in various international congresses to share good practice experience, information about animal welfare and 3Rs initiatives.

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Question: What is being done to implement rapidly and enforce across Europe the revised European Directive 2010/63/EC on the protection of animals used for scientific purposes?

Now that the new Directive 2010/63 is in place, EFPIA and its member companies continue to play a leading role in driving its implementation at EU and national levels. EFPIA Research and Animal Welfare Group representatives participate in European Commission-led expert groups that address some of the 'grey zones' left in the text when the political compromise was set such as statistical reporting, genotyping, education and training, inspections, project evaluation and retrospective assessment, lay summaries, and so forth. These are directly relevant to the implementation, promotion, and enforcement of 3Rs and welfare principles and increased transparency. In 2014, EFPIA held a workshop with public and private research organisations to identify areas that would benefit from greater training and dissemination support from the scientific community. These include authorisations and ethical review processes, dissemination of 3Rs information and implementation of new statistical reporting requirements.



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Question: How do we contribute to an open and constructive dialogue on animal welfare?

On World Day for Laboratory Animals (April 24th), an annual seminar is organised by numerous animal welfare groups in Denmark. One of our members in Denmark participates actively in these events either as a presenter and/or in discussions. In 2013, it held a workshop demonstrating the housing of rats and in 2014, two presentations were held, one showing a video of a refinement initiative in a pig study.

The pharmaceutical industry continues to work in collaboration with the UK NC3Rs (National Centre for the Replacement, Refinement and Reduction of Animals in Research) and participates in the CRACK-IT challenge. The CRACK-IT challenge is a two-phase competition that funds collaborations between industry, academics and SMEs to solve problems related to the 3Rs, leading to new products or improved business processes. The brochure **“Working with the Pharmaceutical Industry”** gives an overview of 10 years of collaboration thus far.

Participation in collaborative platforms is another channel used for communicating on

the 3Rs. For example, EFPIA is a member of the European Partnership for Alternatives to Animal Testing (EPAA). EPAA is an unprecedented voluntary collaboration between the European Commission, European trade associations, and companies from seven industry sectors. The partners are committed to pooling knowledge and resources to accelerate the development, validation and acceptance of alternative approaches in regulatory testing. EPAA organizes an annual conference, each time focusing on a particular aspect of 3Rs. In 2013 the leading theme was: **“More Predictive Safety Science for a More Competitive Europe”**.

The presentations and video recording of the conference are available on the [EPAA website](#).



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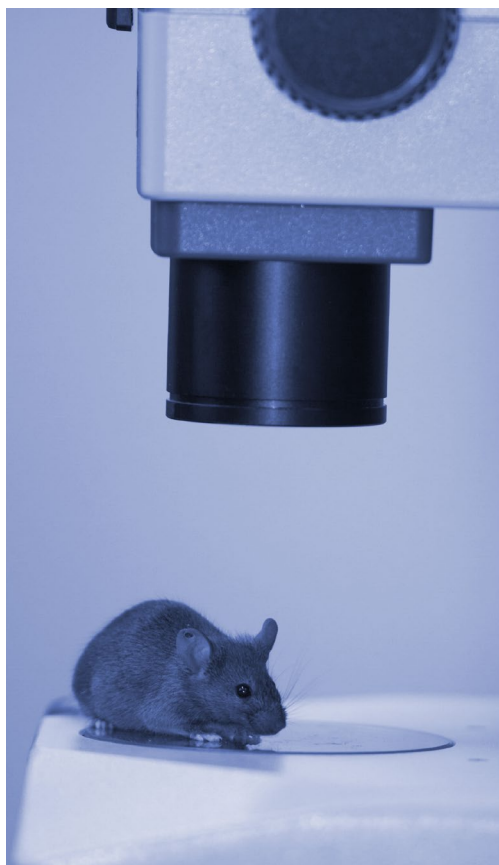
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Question: How is industry communicating the progress made in animal welfare activities, specifically the 3Rs?



Besides participating in international events and platforms, the pharmaceutical industry is communicating on the 3Rs through Corporate Social Responsibility (CSR) reports. Each pharmaceutical company has a website where CSR reports are available. A dedicated section on animal welfare and the 3Rs are included in these reports. A few examples can be found here:

- AstraZeneca
- GlaxoSmithKline
- Novartis
- Novo Nordisk
- Merck
- Sanofi
- UCB

EFPIA and some of its member companies produce an annual 3Rs report illustrating industry's commitment to applying the 3Rs principles in animal research and to enhancing scientific advances leading to the implementation of one of the 3Rs. EFPIA has already produced two reports in 2011 and 2012. These reports are available on the [EFPIA website](#).

28 years ago, Interpharma, the Swiss Pharmaceutical industry Association, created a **3Rs Foundation**, the objective of which is to support the development and application of the 3Rs through financial support, wherever possible, to research the possibilities of reducing, refining or replacing animals in research. The publication (available in English, French and German) **"3R – une recherche de qualité moins d'expérience sur les animaux"** explains the principle of 3Rs, what the achievements in this field are, and the limitations of alternatives, with the aim of opening dialogue on this sensitive subject.

In 1986 the VFA, the Association of Research-Based Pharmaceutical Companies in Germany, together with the German Agricultural Ministry, the "German society for the protection of animals" (Deutscher Tierschutzbund), the Association of the Chemical Industry (VCI) and other Associations founded the SET (German: Stiftung Ersatzmethoden Tierversuche). The SET Foundation helps industry, animal

welfare organisations, research bodies and government to co-ordinate their efforts and work together towards a common goal: the refinement, reduction, and replacement of animal experiments through the active development of 3Rs methods. In this regard, the SET Foundation supports eligible projects, aiming to reduce the number of animals used and/or their distress as effectively and broadly as possible. Information on the SET Foundation and the supported projects can be found on the SET Foundation website in English at:

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Useful Links

Accreditation of Laboratory Animal Care International (AAALAC) - www.aaalac.org

Alternatives Approaches to Animal Testing (EPAA) - www.epaa.eu.com

European Centre for the Validation of Alternative Methods (ECVAM) – www.ecvam.jrc.it

Federation of Laboratory Animal Science Associations (FELASA) - www.felasa.eu

Innovative Medicines Initiative (IMI)- www.imi.europa.eu

Institute for Laboratory Animal Research (ILAR)- www.dels.nas.edu/ilar

European Commission - http://ec.europa.eu/environment/chemicals/lab_animals/home_en.htm

National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs) - www.nc3rs.org.uk

3R Foundation - www.forschung3r.ch

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Photos have been sourced from a number of sources, including EFPIA and Understanding Animal Research. EFPIA would like to thank the members of the EFPIA working group on Research and Animal Welfare for the valuable contributions to this report.