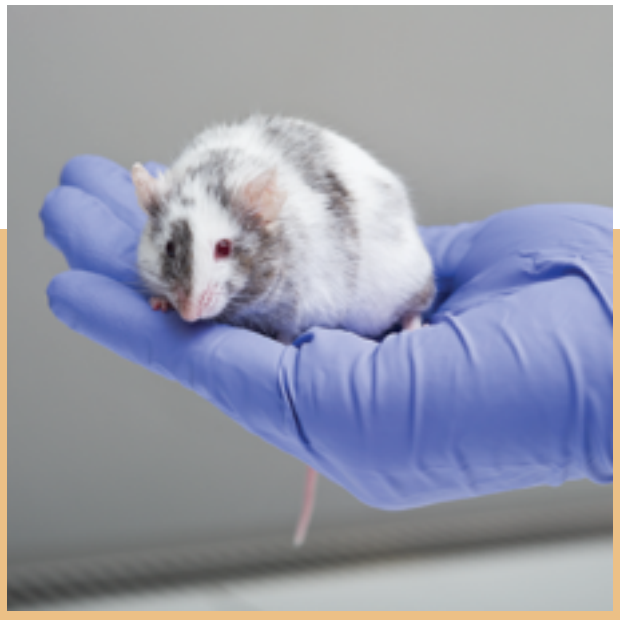
Home Office

Department for Business Innovation & Skills

Department of Health

Working to reduce the use of animals in scientific research



Acknowledgements

This Delivery Plan has been developed in collaboration between the Home Office Animals in Science Regulation Unit (ASRU), the Department for Business, Innovation and Skills (BIS) and Government Office for Science. It reflects significant input from other government departments including the Department of Health (DH), the Department for Environment, Food and Rural Affairs (Defra), the Food Standards Agency (FSA) and the Foreign & Commonwealth Office (FCO) as well as a number of government agencies including Public Health England (PHE), the Medicines and Healthcare Products Regulatory Agency (MHRA), the Veterinary Medicines Directorate (VMD), the Animal Health & Veterinary Laboratories Agency (AHVLA), the Food & Environment Research Agency (Fera), the Centre for Environment, Fisheries & Aquaculture Science (Cefas) and the Health & Safety Executive (HSE). The National Centre for the Replacement, Refinement & Reduction of Animals in Research (NC3Rs) has made a major contribution. The Government Chief Scientific Adviser and departmental Chief Scientific Advisers, as well as experts from academia, the Research Councils and several government advisory committees, have also contributed significantly to this work.

First published: February 2014
URN BIS/14/589
ISBN 978-1-78246-264-4

Foreword

The Programme for Government commitment to work to reduce the use of animals in research brings together the UK's long tradition of support for animal welfare alongside its strength in science and innovation. This document provides more detail on how we will continue to deliver our commitment while maintaining and reinforcing our position at the forefront of global science and innovation.

In this Plan, we bring together new and existing initiatives for promoting the widespread adoption of scientific and technological advances which present significant opportunities to replace animal use, to reduce the number of animals used and to refine the procedures involved so as to find additional ways to minimise suffering.

Delivery of this Plan is not simply a challenge for the Government and its agencies. If we are to be successful we need to enhance our partnerships with a wide range of stakeholders including the research community in both academia and industry and others with relevant animal research and welfare interests.

The UK is seen as a leader, globally, in the adoption of the 3Rs. This gives us a real opportunity to accelerate the international uptake of scientifically valid alternatives in research and safety testing. This work is very challenging and often involves agreement at inter-governmental level. However, the reward is to effect reductions in the volume of animal experiments on a scale well above what can be achieved by domestic action alone. It will also benefit the UK Life Sciences sector (a key component of the Government's Industrial Strategy) by ensuring that strict application of UK regulations does not simply export experiments abroad. Similarly, harmonising standards internationally will ensure that UK companies with high welfare standards are not shut out of large developing economies which may currently demand additional animal testing not required by most states.

Transparency and openness about the use of animals in research, and why their continued use remains necessary, helps to improve our overall understanding about the issue, enables an informed public dialogue and can help to mitigate anxieties and misunderstandings. An important part of our overall strategy is to build on the Declaration of Openness launched last year, driven by the academic sector, health charities and industry. This commits those engaged in research to foster an environment of openness around the ways in which animals are used in scientific research in the UK.

Through this Delivery Plan, we demonstrate how placing 3Rs approaches at the heart of a science-led programme will assure high standards of animal welfare while continuing to deliver benefits for humans, animals and the environment and UK economic growth.

The Rt Hon David Willetts MP
Minister for Universities and Science
Department for Business, Innovation and Skills

Lord Taylor of Holbeach CBE
Lords Minister and Minister for Criminal Information
Home Office

The Rt Hon Earl Howe
Minister for Quality
Department of Health

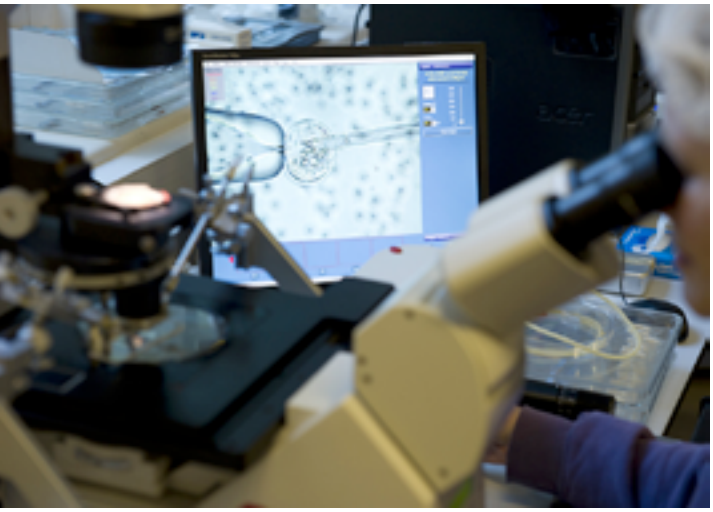
Contents

Introduction

The use of animals in scientific research remains a vital tool in improving our understanding of how biological systems work both in health and disease. Such use is crucial for the development of new medicines and cutting edge medical technologies for both humans and animals, and for the protection of our environment. Hence, enabling properly regulated use of animals is essential to improving the health and lives of humans and animals and to the safety and sustainability of our environment.

Our National Health Service is one of the primary beneficiaries of research and testing using animals – such as through the licensing of new medicines, the development of new and safe vaccines and for the detection and control of infectious diseases.

For example, the development of monoclonal antibody therapies over the last 20 years has completely transformed our ability to treat diseases including breast and other cancers, rheumatoid arthritis and multiple sclerosis. The development of this technology would not have been possible without the use of animals both in developing the fundamental elements of the technology and in producing the medicines used to treat patients.



Aside from improving quality of life, this research supports the UK's world-class research base in environmental, agricultural, medical and other life sciences. This in turn will improve the prospects of patients and animals in the UK benefiting from the outcomes of research.

It also supports a number of highly skilled jobs through a strong academic research base and an attractive regulatory environment. Economically the life sciences sector contributes over £50bn a year to the UK economy with agriculture contributing £9bn and it underpins the UK's £26bn sector providing us with healthy and wholesome food.

Underpinning all of this research is a strong commitment to maintaining a rigorous regulatory system which ensures that animal research and testing is carried out **only** where no practicable alternative exists, and under controls which keep suffering to a minimum. This is achieved through robustly applying the principles of the 3Rs – principles first advocated in the UK over 50 years ago[1] – to all research proposals involving the use of animals.

Implementing the 3Rs requires that, in every research proposal, animals are **replaced** with non-animal alternatives wherever possible; that the number of animals used is **reduced** to the minimum needed to achieve the results sought; and that, for those animals which must be used, procedures are **refined** as much as possible to minimise their suffering.

It is in this context that in 2010, the Government made a commitment to work to reduce the use of animals in scientific research. This commitment is not focused

1 Russell & Birch (1959) The Principles of Humane Experimental Technique. http://altweb.jhsph.edu/pubs/books/humane_exp/het-toc

on baseline numbers which are influenced by a range of extraneous factors. Instead, it encompasses replacement, reduction and refinement (the 3Rs) more broadly, putting them at the heart of a science-led approach.

The scientific imperative for developing new approaches to research and development is very strong. Although the use of animals forms a major part of much scientific and medical research, success seen in animal studies has not always translated in the clinic. Many potential drugs fail due to lack of efficacy in humans or concerns about their safety. Methods are needed to screen these failures out as early as possible and to select, with further research and development, those approaches most likely to succeed.

Similarly, there are concerns about the utility of animal studies for testing environmental chemicals. For example, animals are invariably exposed to much higher doses than typical human exposures making interpretation difficult. A number of international science organisations have called for the development of mechanism-based assays that are more predictive of human biology. Increasingly attention has focused on non-animal technologies for solutions. These include tissue engineering, stem cells, and mathematical modelling – areas in which the UK science base is at the forefront.

There is an opportunity to both minimise the use of animals and address major challenges faced by society, such as problems associated with ageing. By tapping into the UK's strong science base it is possible to derive economic benefits from the development of new models and tools which replace, reduce or refine the use of animals in research.

In a Written Ministerial Statement on 18 July 2011[2], we set out our ambition to deliver the commitment through such a science-led programme, spearheaded both by relevant government departments and agencies, working together where appropriate, and by the National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs), an organisation with a strong record in promoting the 3Rs in animal research.

In this Delivery Plan we explain that we will remain strong advocates for this research given its importance in helping us to combat disease and improve lives and outcomes for patients and their families. We set out the detail of how we are delivering against the ambition to work to reduce the use of animals in research engaging with the academic sector, health charities and industry as well as animal welfare bodies.

Our Plan demonstrates how we are taking advantage of technological developments, including massively increased computer power and wider scientific innovation, to provide the perfect environment and catalyst for scientific change and progress which will help to reduce the use of animals in research.

2 http://www.publications.parliament.uk/pa/cm201011/cmhansrd/cm110718/wmstext/110718m0001.htm#1107182000388

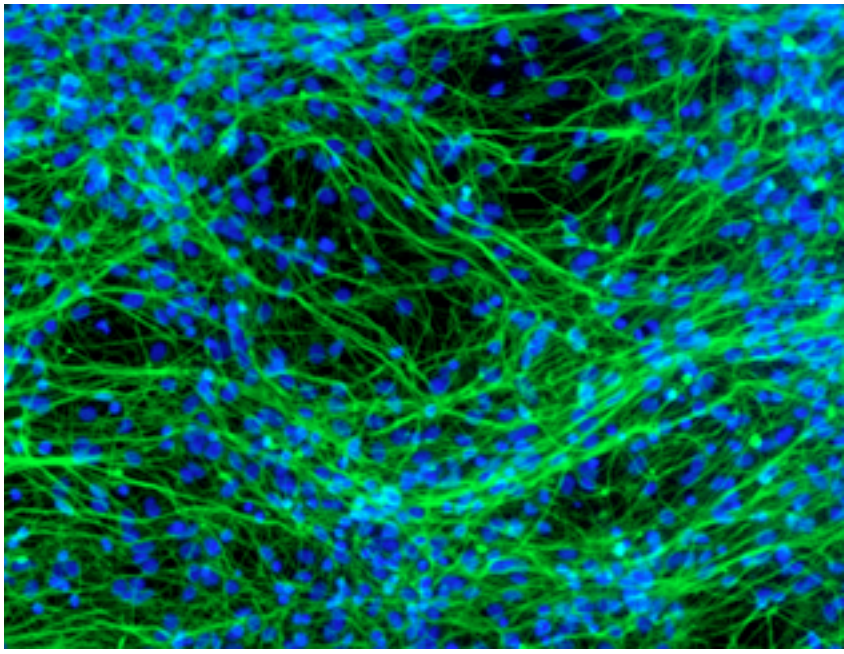
It includes actions we are taking directly and collaboratively across government, and describes how we are working with our key partner organisation, the NC3Rs, and others to deliver the commitment. The Delivery Plan sets out the Government's three strategic priorities in delivering the commitment by putting the 3Rs at the heart of a science-led programme:

- advancing the use of the 3Rs within the UK;
- using international leadership to influence the uptake and adoption of 3Rs approaches globally; and
- promoting an understanding and awareness about the use of animals where no alternatives exist.

Each of these strategic priorities is considered in detail in Section 2 of this Delivery Plan.

In our Strategy for UK Life Sciences published in 2011[3] we set out our aim to make the UK the location of choice for pioneering research and development together with investment in the related manufacturing. This Delivery Plan shows how implementing the 3Rs makes a real contribution to this strategy, realising significant benefits for humans, animals and the environment and sustained economic growth.

A consequence of the commitment in the Coalition Agreement to work to reduce the use of animals in scientific research has been, and will continue to be, to accelerate uptake of the 3Rs both domestically and internationally. This success is based upon the premise that the 3Rs provide opportunities for high standards of animal welfare alongside better science, faster science, and more cost-effective science. With this in mind, we have designed a package which is good for patients and their families, good for science, good for animal welfare and good for our economic growth. We will review progress on this Delivery Plan 12 months after publication and regularly thereafter.



Neurons derived from human neural stem cells.
Credit Yirui Sun, Wellcome Images

3 https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/32457/11-1429-strategy-for-uk-life-sciences.pdf

Section 1
Setting the Scene

1.1 The continuing need to use animals in research

The Government is clear that there is a continuing need for properly regulated and ethically conducted research using animals where the harm caused to the animals is justified by the potential benefits, and where no practicable alternative exists. We will continue to make this case and to improve understanding and awareness of this issue.

This principle is of fundamental importance to many sectors including:

- ***The life sciences sector.*** Factors such as the rapid pace of global travel, the looming threat of widespread anti-microbial resistance, and an increasingly ageing world population, all present challenges which impact on both human and animal health and are importantly reflected in the global One Health Initiative[4]. Improved research models will be required in dealing with the prevalence of conditions such as pandemic flu, drug-resistant TB, dementia and the increased burden of obesity and related conditions such as diabetes, stroke and heart disease. Animal research will play a vital role in delivering these challenges.
- ***The animal welfare sector.*** The aim to improve the husbandry and care of farmed, companion, laboratory, zoo and other managed animals through approaches which minimise pain, suffering, distress or lasting harm depends on research, often in those species.
- ***The environmental sector.*** Understanding the potential impact of chemicals, both naturally occurring and synthetic, on our environment is critically important. Whilst many non-animal tests have been developed in recent years, there remains a need for animal tests to ensure the safety of human and wildlife populations.

As a consequence, the UK requires the use of a significant number of animals in scientific experiments or procedures each year (see Figure 1) and this Plan provides the opportunity to set out a more detailed explanation and justification for their use and the benefits that result. In 2012, over 4 million procedures were commenced, significantly lower than the volumes in the 1970s and early 1980s, but higher than the figures in the 1990s and 2000s.

4 http://www.oie.int/fileadmin/Home/eng/Current_Scientific_Issues/docs/pdf/FINAL_CONCEPT_NOTE_Hanoi.pdf

Box 1: The positive impact of research involving animal experiments

- Zebrafish have been found to share a highly conserved form of the key ion channel susceptible to disrupting QT interval length (biomarker for cardiac arrhythmia and sudden death) with humans[1]. Scientists have taken advantage of this similarity to use zebrafish as an effective model to test the propensity of drug compounds to induce cardiac arrhythmias in human patients.
- Researchers at the MRC Toxicology Unit at University of Leicester have developed a genetically modified strain of mice to model human neurodegenerative disease. Study and manipulation of the mouse model has led to the identification of an orally administered drug compound that can correct the disease pathway and prevent neurodegeneration[2].
- Researchers at Cambridge University discovered that deleting the KSR2 gene in transgenic mice caused them to experience extreme weight gain. Defects in this gene have now been shown to be responsible for abnormal metabolism in humans offering a potential therapy for obesity and Type 2 diabetes[3].
- The use of non-human primates in Parkinson's Disease research has been invaluable in identifying the subthalamic nucleus as a surgical target for deep brain stimulation in human patients. This work was initially carried out at the University of Oxford and has since progressed through human trials to become an effective treatment for reversing the debilitating tremors experienced by Parkinson's patients[4].

1. Arnaout, R. *et al.* (2007) Proc. Natl. Acad. Sci. 104(27):11316-21
2. Moreno, J. A. *et al.* (2013) Sci Transl Med. 5(206):138.
3. Pearce, L. R. *et al.* (2013) Cell. 155(4):765-77.
4. Parkin, S. *et al.* (2001) Stereotact. Funct. Neurosurg. 77:68-72.

Figure 1 shows the scale of animal use in research since 1945. Use has increased steadily and dramatically since 1945 and peaked around 1970 at a total of over 5.5 million experiments. In 1987, the methodology for counting the number of animals used in research changed from counting only experiments to counting the whole range of scientific procedures. This meant that the breeding of genetically altered (GA) animals (mainly mice and fish) was included and this now accounts for almost half of procedures (48% in 2012). When the number of GA animals is separately identified within the totals over the last 20 years (Figure 2), it is clear that the numbers of animals used in non-breeding procedures has declined overall from 2.4 million in 1995 to 2.13 million in 2012.

Apart from breeding, the most common use of animals in research is for fundamental and applied studies in human medicine[5]. This can help us to better understand the pathways and causes of disease and, for example, bring forward the development of medicines and vaccines to help save lives and improve outcomes for

5 Includes human dentistry.

Figure 1. Experiments or procedures commenced each year, 1945–2012.

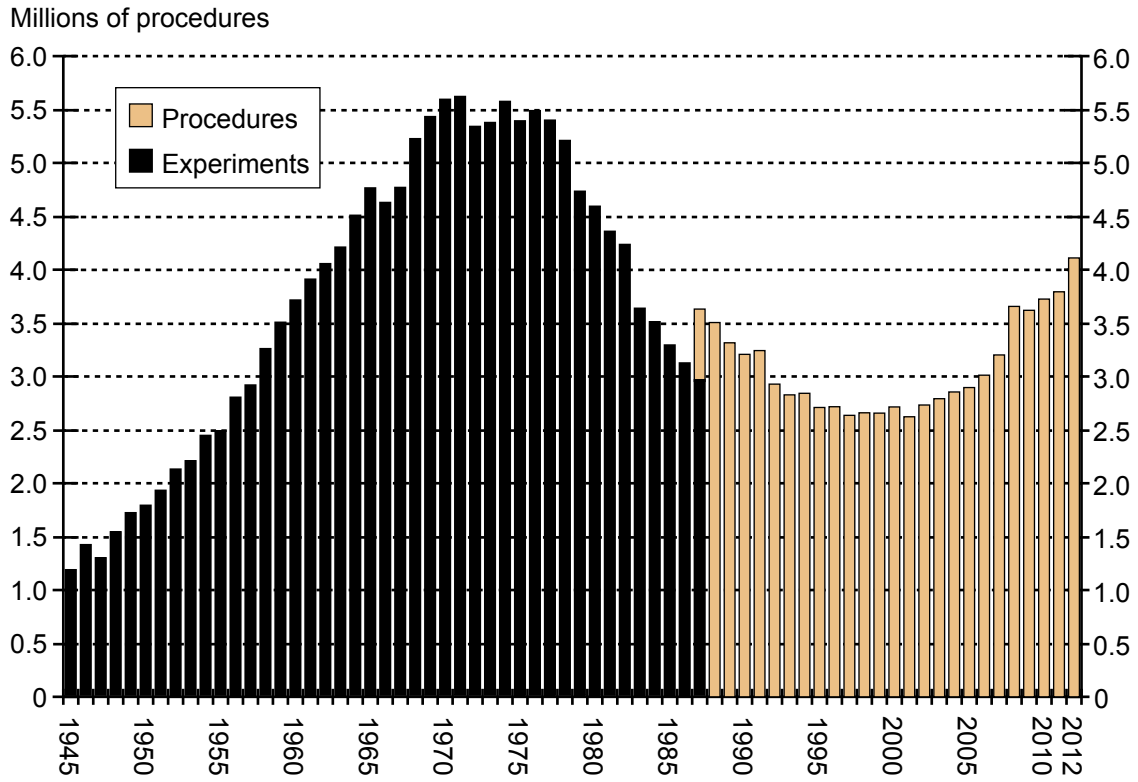


Figure 2. Animal procedures showing breeding separately since 1995.

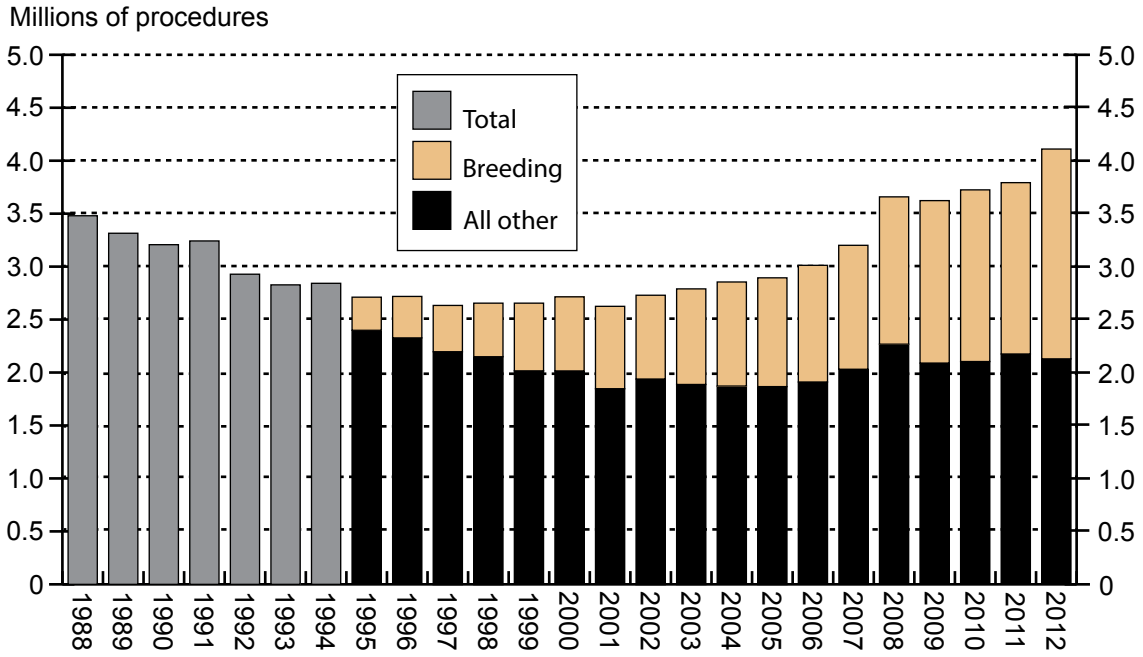
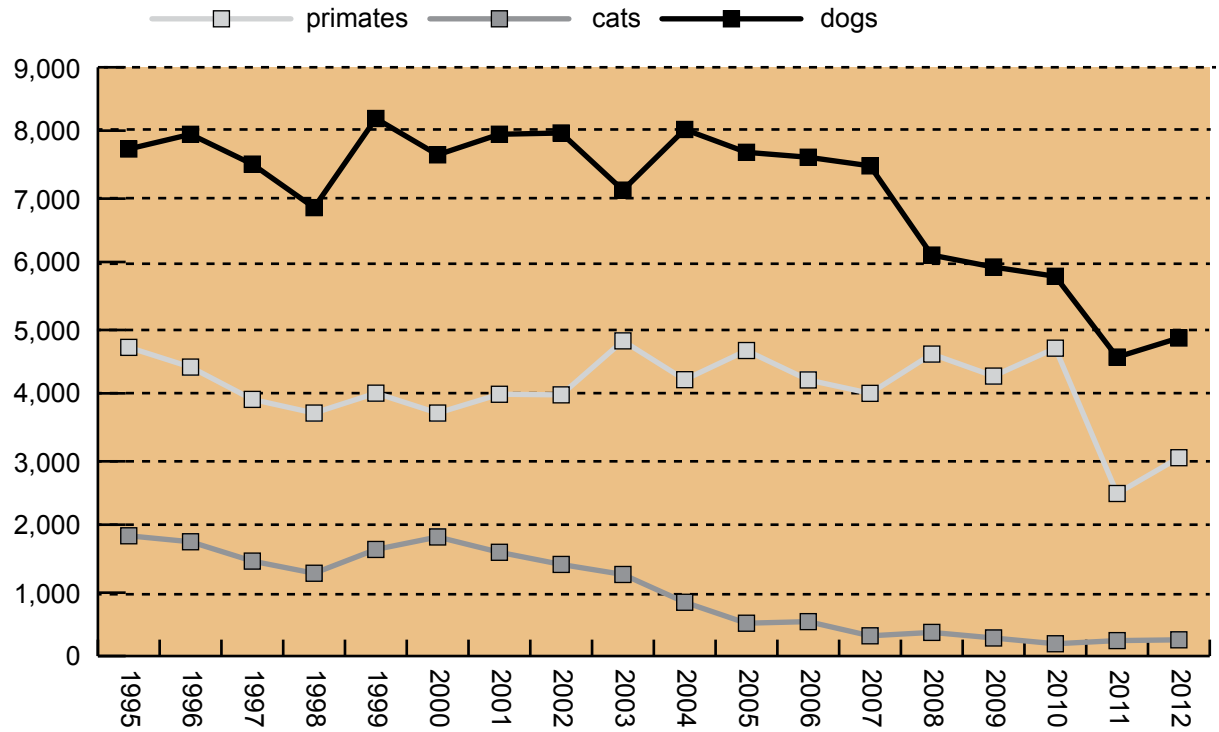


Figure 3. Procedures commenced each year on dogs, cats and non-human primates since 1995.



patients. Rodents (such as mice and rats), fish and birds account for over 98% of all procedures. In 2012, just over 4,800 procedures involved dogs (0.12%), mainly beagles, and 3,000 involved non-human primates (0.07%). In both cases, the majority were used for safety testing of human medicines. A small number of procedures involving primates were to aid our understanding of brain function and disease in humans. Cats were used in 247 procedures (0.006%), the majority in nutrition studies for the benefit of cats. The main fields of research using animals were immunology (576,000) and cancer research (501,000). Toxicology accounted for just over 9% of procedures (377,000), mainly using rodents and fish and none involving the testing of cosmetics or household products.

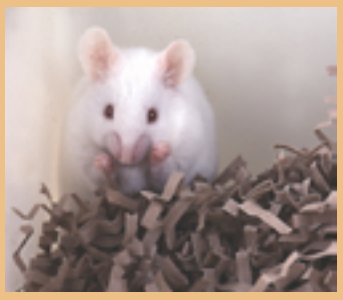
As the research potential offered by genetically altered rodents and fish has increased, so the number used has risen significantly and this is reflected in total numbers between 1995 and the present. However, the trend for many other species – for example dogs, cats and non-human primates – has generally declined over the same period (see Figure 3) since much work previously done in these species can now be done on species of perceived lower sentience such as mice or fish.

Scientists are required to use the species of the lowest perceived sentience which is appropriate to their research. However, this may lead to an increase in the overall numbers used. For example, neuroscience studies in a small number of non-human primates may be replaced by a genetically altered mouse model in which significantly greater numbers of animals need to be used.

Box 2 outlines an example in which scientists have developed a way of replacing one species with another of perceived lower sentience in their research.

Advances in genetics and understanding the genome are likely to lead to a continued increase in the use of genetically modified animals (mainly mice and fish) as scientists seek to better understand gene functions and interactions. This research will be essential to finding potential new targets for treating diseases such as dementia and type 2 diabetes. It will also underpin the development of stratified or personalised medicines

Box 2: An example of replacing non-human primates with transgenic mice



Transgenic mice have been used to replace non-human primates in oral polio vaccine safety tests. Polio vaccine utilises live attenuated virus particles and it is essential that each batch of vaccine is tested to ensure that it is safe and does not revert to infectious virus on use. Non-human primates possess virus receptors similar to those found in humans. However, mice have now been genetically modified to express human polio receptors. This mouse model has now been validated and formally adopted by the European Pharmacopoeia[1].

1 http://www.animalresearchforlife.eu/Replacing%20Primates%20by%20Transgenic%20mouse%20for%20polio%20vaccine%20testing.pdf

which target diseases, such as specific types of cancer, based on a detailed understanding of a patient's genetics and their condition.

Recognising this potentially very significant increase, the UK is playing a major role in international programmes (e.g. the International Mouse Phenotyping Consortium[6]) which ensure that such genetically altered strains are characterised and shared globally, hence maximising their scientific potential whilst minimising the possibility of duplication.

It is important to note that the annually published statistics count the number of animals *which have been used* in procedures. They do not count the number of animals *which have not needed to be used* as a result of implementing the 3Rs to replace and reduce animal use. Monitoring success in implementing the 3Rs is therefore dependent on reviewing case studies. We provide a number of such case studies in this Delivery Plan, and others are published by those who fund this research such as NC3Rs. Unfortunately no recognised system exists for assessing the 'unit of benefit' to humans, animals and the environment for each animal used in research, and how this has improved over time.

A further important absence from the data currently recorded is a measure of the actual severity which is experienced. We are committed to correcting this in 2014 to give greater transparency to the public about what level of suffering really occurs and therefore improve awareness and understanding about how animals are used in research and the impacts of it. In many cases, this will show the severity of procedures to be mild or less than predicted (e.g. in breeding of many genetically altered strains). Further, this will also help us to increasingly focus 3Rs attention on those procedures which cause the greatest severity.

Nevertheless, it is no simple task to either predict or contain the number of animals which will be used in future years. On the one hand global economic and scientific trends, with demands for even better medicines and environmental management, may lead to upward pressure. On the other hand implementing the 3Rs through new technologies which enable scientists to use better, faster and cheaper non-animal approaches will lead to downward pressure.

In this context, a key priority for the Government is to ensure that we continue to maintain our high standards through rigorous regulation of the use of animals in research, and we avoid exporting work overseas to countries where welfare standards may be lower.

1.2 What the Government is doing to promote the 3Rs

1.2.1 Promoting science and innovation in the 3Rs

The UK plays a leading role globally in supporting the development and adoption of techniques to replace,

6 www.mousephenotype.org

reduce and refine the use of animals. For example, the Government has been providing funding to the NC3Rs since it was established in 2005 and the level of that funding has significantly increased since 2010 based upon their record of success. The Government's research funding bodies (e.g. the Medical Research Council) have funded major initiatives, often in partnership with charities such as the Wellcome Trust, to ensure the UK gives leadership in data sharing to avoid duplication occurring and to help improve understanding, for example about the pathways and causes of disease. Furthermore, a number of government departments and agencies have, in recent years, worked collaboratively to develop and validate new technologies which can replace animal use in safety testing and help reduce risks to the public, the environment, pets and farm animals.

Examples of how NC3Rs puts the 3Rs into practice are set out in Box 3.

Increasingly scientists are using both non-animal (*in vitro*) methods and animal-based (*in vivo*) methods in a sequential manner. This approach realises the benefits of the faster and more cost-effective progress which *in vitro* methods can often deliver whilst also addressing the complexity which only an appropriate whole animal *in vivo* model can offer.

Recent advances in genetic manipulation and generation of clinically relevant cell lines for drug testing and disease modelling have significantly impacted on the use of animals in research. In pursuing technology that will help to reduce the number of animals used in research, scientists in the UK have generated tools that are invaluable to the study of human development and disease placing us at the forefront of innovation and technology internationally.

Box 3. The 3Rs in practice

Animal welfare: The NC3Rs champions animal welfare and high standards in animal research. It has funded research to improve the assessment and alleviation of pain in laboratory animals, and to ensure that rats and mice are killed as humanely as possible at the end of studies. The Centre reviews all applications submitted to the major bioscience funding bodies that involve the use of non-human primates, cats, dogs or horses, identifying opportunities to further implement the 3Rs. It also hosts an annual meeting for scientists, vets and animal care staff who use non-human primates to discuss welfare issues; recent meetings have included topics such as training animals to cooperate with procedures such as blood sampling in order to minimise any stress they might experience and the use of imaging technologies.

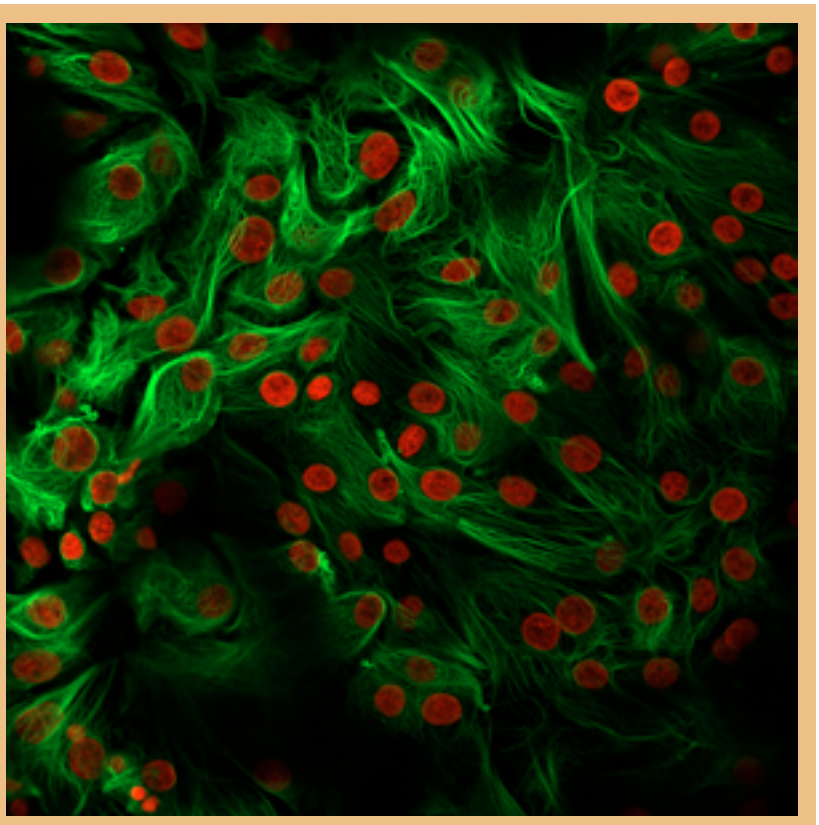
Training and development: The NC3Rs supports the training and development of early career scientists so that the 3Rs are embedded in mindset and practices of the next generation of research leaders. This includes a PhD studentship scheme which is dedicated to the 3Rs and a scheme for early career post-doctoral scientists (the David Sainsbury fellowship) which supports the transition to independent researcher. To date the NC3Rs has funded 37 PhD studentships and six David Sainsbury fellowships.

Box 4. Use of induced pluripotent stem cell (iPSC) technology

Progress in the field of induced pluripotent stem cell (iPSC) biology has led to the generation of patient matched cell lines for use in diagnosis, treatment and study of disease *in vitro*.

For example, iPSC lines have been generated from patients suffering from congenital liver disease. They have then been genetically manipulated to correct the mutation and effectively cure the disease in the cells[1]. These cells are invaluable for studying the disease and its effect on human liver cells, work that in the past could only have been modelled in animal systems.

1. Yusa, K. *et al.* (2011) Nature. 478(7369):391-4



Human induced pluripotent stem cell derived hepatocytes (liver cells) in vitro.

Credit: Richard Gieseck III, University of Cambridge

Box 4 describes one way in which cutting edge genetic manipulation and clinically relevant cell types are being used to replace animals in research. Reprogramming mature cells to become pluripotent offers enormous promise for the future in enabling potential human therapies to be tested in relevant cells of many types derived from the target species. The technology has significant implications for the 3Rs by enabling more widespread use of human tissues. UK leadership in this field was recognised by the 2012 Nobel Prize awarded jointly to Sir John Gurdon and Shinya Yamanaka.

1.2.2 A regulatory framework which enshrines the 3Rs

At the forefront of any decision to use animals in research is the need for robust evidence to justify the use of animals. The UK's regulatory system[7] is geared to prevent animals being used where a practicable alternative exists and those licensed to carry out research using animals must ensure that their proposals comply fully with the principles of the 3Rs. It also requires a harm-benefit analysis of all research proposals to ensure that any harm that may be caused to the animals in terms of suffering, pain and distress is justified by the expected benefits for humans, animals or the environment. This analysis is conducted by Home Office inspectors, all with veterinary or medical qualifications and special expertise in assessing research proposals.

In addition, the proposal must have been considered by the research establishment's Animal Welfare and Ethical Review Body (AWERB) to confirm that the

7 https://www.gov.uk/research-and-testing-using-animals

necessary facilities and staff are available to care for the animals properly, that the 3Rs have been effectively implemented in the proposal, and that the work is considered locally to be acceptable from an ethical perspective.

During 2012, the UK regulatory system was reviewed in line with a new European Directive[8] with the aim of both promoting the 3Rs and improving animal welfare through harmonising standards across Europe.

1.3 Challenges to delivery

Whilst significant efforts are being made by government, academia, industry, research funders and animal welfare bodies to advance the 3Rs, there are also challenges to making rapid progress. Many of these relate to the need for as yet undiscovered technologies, but others may relate to conservatism and a risk-averse approach to adopting change. In developing this Delivery Plan, we have confronted these challenges head on to set out ways to address them. We take the opportunity to set out how research involving animals can also bring benefits for all of us and we aim to improve understanding of why this is the case.

A challenge for academia is conservatism on the part of journal editors and peer-review panels to accept publications based on non-animal techniques in lieu of the "traditional" animal models. Publications such as NC3Rs' ARRIVE[9] Guidelines in 2010, and the now widespread adoption of these guidelines by a significant proportion of international journals, have raised awareness of this issue as well as the need to improve standards of reporting study design and analysis. This is impacting standards of peer review and publication practices internationally.

Within the pharmaceutical industry, licensing of new medicines such as new treatments for cancer and heart disease is tightly regulated at both national and international level by agencies such as the UK

Medicines and Healthcare Products Regulatory Authority (MHRA) and the European Commission. However, the need for new medicines is global and, in order to market their products widely, pharmaceutical companies must satisfy the testing requirements of all countries. Hence, even when the UK has accepted a validated non-animal test, the animal test may still need to be performed to satisfy another country or region. Furthermore, if the UK reacts unilaterally in banning the animal test, the work is likely to move overseas where welfare standards may be lower.

An international effort to address this dilemma lies in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH[10]) which aims to reach agreement between Europe, the USA and Japan for revised pharmaceutical safety testing guidelines which minimise the use of animals. ICH has also granted observer status to many other countries – and these are encouraged to adopt the revised guidelines once agreed. The International Cooperation on Harmonisation of Technical Requirements for

8 EU Directive 2010/63 on the protection of animals used for scientific purposes. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:276:0033:0079:EN:PDF

9 http://www.nc3rs.org.uk/page.asp?id=1357

10 www.ich.org

Registration of Veterinary Medicinal Products (VICH[11]) fulfils a similar function for veterinary medicines.

Likewise, testing on animals helps to ensure the safety of food and environmental chemicals. The evaluation of the safety of food and environmental chemicals is undertaken by bodies such as the UK Food Standards Agency and Health & Safety Executive, the European Food Safety Authority and the European Chemicals Agency. At an international level, the Organisation for Economic Co-operation and Development (OECD)[12] sets out the standards which must be satisfied to give assurances of safety, and to permit international transport of bulk chemicals. Significant efforts are being made by OECD (e.g. the Adverse Outcomes Pathways initiative) to enable sharing of the massive amounts of data being generated globally following testing on animals on the toxicity of environmental chemicals, and to ensure future practices to safeguard our environment are based upon best practices and minimising the use of animals as much as possible.

Progress in changing regulatory testing guidelines can be frustratingly slow since regulators are understandably averse to adopting changes until they have absolute confidence that the risks to humans, animals and the environment are not being increased. In this Delivery Plan we focus on opportunities to enhance our influence in both ICH and OECD discussions and to accelerate changes where they are supported by sound evidence. We are identifying key partners (e.g. in the EU, USA, Japan, China and Brazil) with whom we can work at a diplomatic as well as a scientific level to catalyse our impact as well as ensuring that our Plan increases openness and transparency about how and why animals are used in research.

1.4 Who needs to be involved?

Everyone has a part to play. Government can provide support and leadership to help to minimise the use of animals in research and help to make the case for why

animals need to be used when no alternative exists. We can therefore improve public understanding of why we need to use those animals.

This must involve all the relevant central government departments including the Department of Business, Innovation and Skills (BIS) which supports those who deliver this research, the Department of Health (DH) and the Department for Environment, Food & Rural Affairs (Defra) which both benefit from the outcomes of this research, and the Home Office which regulates this research. Agencies and non-ministerial departments across government also have an important role to play e.g. Public Health England (PHE), the Food Standards Agency (FSA), the Health & Safety Executive (HSE), the Medicines and Healthcare Products Regulation Agency (MHRA), the Centre for Environment, Fisheries & Aquaculture Science (Cefas) and the Veterinary Medicines Directorate (VMD). The Foreign & Commonwealth Office (FCO) provides important support in addressing many of the international challenges.

11 http://www.vichsec.org/en/what-is.htm

12 www.oecd.org

The involvement of our key delivery partner, NC3Rs, is crucial to this work. The majority of funding for the NC3Rs currently comes from BIS through ring-fenced science and research funding allocated by the Medical Research Council (MRC) and the Biotechnology & Biological Sciences Research Council (BBSRC). In addition, other government departments (e.g. Home Office, and Defra) and the Technology Strategy Board (TSB), as well as industry and charities, provide funding either on an on-going basis or for specific projects.

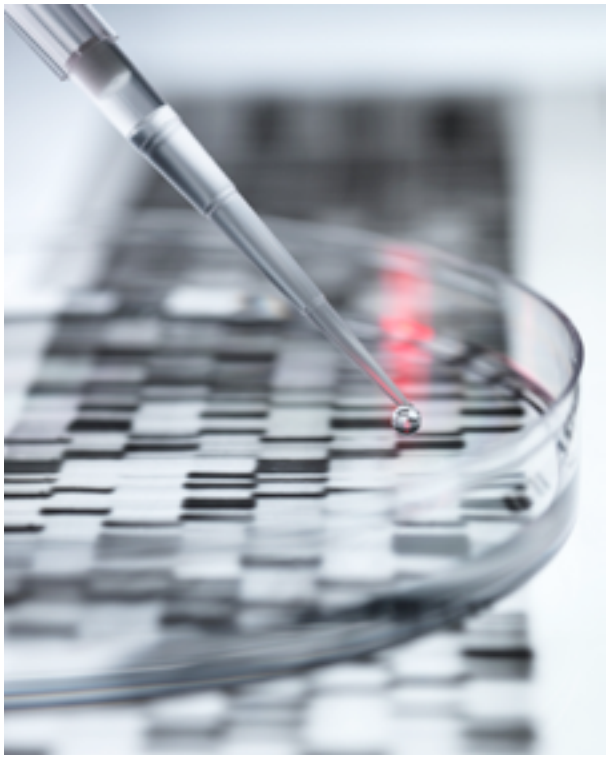
The NC3Rs operates both domestically and internationally as an independent organisation. It has established a strong record of effective interactions with both academia and industry to promote alternative methods based upon sound scientific evidence. NC3Rs works with a wide range of partners to develop specific programmes and schemes. It publishes an annual report highlighting its successes[13] and is very highly regarded internationally. NC3Rs plays a leading role in the Government's delivery of the 3Rs by setting up an effective framework and changing attitudes.

The MRC and the BBSRC are major public funders of animal research in the academic sector and play a key role in providing incentives for researchers to engage with the 3Rs in the work they fund. Working with the NC3Rs and other funders such as the Wellcome Trust, the Research Councils are exploring ways to enable researchers to make the most of available information and resources to minimise possible duplication. They are also developing schemes to increase the collective knowledge and experience in specific areas of research and to encourage greater scientific and cross-disciplinary collaboration.

Animal welfare and alternatives bodies also have a role to play alongside government in promoting the 3Rs. For example, the RSPCA, through its Rodent Welfare Group, is working with Home Office inspectors, scientists and animal care professionals to identify ways to refine some of the most severe procedures such as mouse models of human sepsis. FRAME (the Fund for the Replacement of Animals in Medical Experiments), with support from Home Office inspectors, has developed training for young scientists to improve their skills in experimental design enabling them to reduce numbers of animals used for the same scientific outcome.

Oversight of the delivery of the Plan is led jointly by the Home Office and BIS through a cross-Whitehall working group with representation from all the relevant partners. The international work is being monitored and supported by an Inter-Ministerial Group on International Animal Welfare.

In the following section, we set out in greater detail the actions we are taking across three strategic priorities to address our Coalition Commitment to work towards reducing the use of animals in research. We also identify the lead partners for delivery of each of these actions and the key milestones as indicators of success. We will review our progress against these milestones a year after publication.



13 http://www.nc3rs.org.uk/document.asp?id=1899

Section 2
Delivering the Plan

This section of our Delivery Plan describes a wide range of measures to promote the 3Rs, both within the UK and internationally, and provide opportunities for researchers and industry to address the 3Rs in their work. The actions include encouraging existing programmes and fostering new, specifically targeted, programmes.

Delivery of the commitment is considered against our three strategic priorities, putting the 3Rs at the heart of a science-led programme:

- a domestic programme which focuses on advancing the use of the 3Rs within the UK;
- an international programme aimed at influencing the uptake and adoption of 3Rs approaches globally; and
- a programme aimed at promoting an understanding and awareness about the use of animals where no alternatives exist.

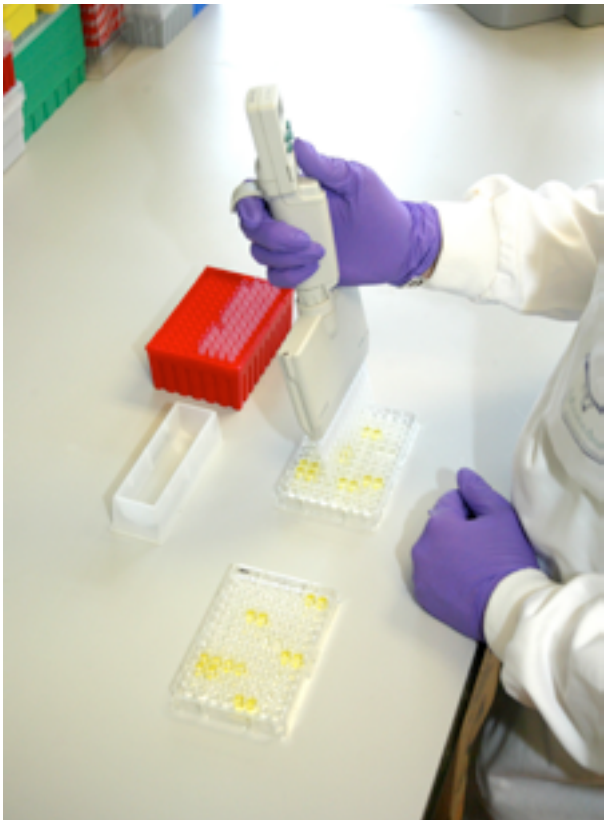
We consider each of these strategic priorities in detail together with specifics of the actions being taken to ensure their delivery, and some key milestones against which success will be measured.

2.1 Advancing the use of the 3Rs within the UK

The UK has a proud track-record of ensuring that the use of animals in research is kept to the minimum whilst also making the case for the benefits that come from that research – consistent with our position as a leading innovator in the life sciences. However, the Government is not complacent and we recognise the need for scientists to constantly strive to minimise both the numbers of animals used and the level of pain or distress experienced by each animal.

Our key objectives are to:

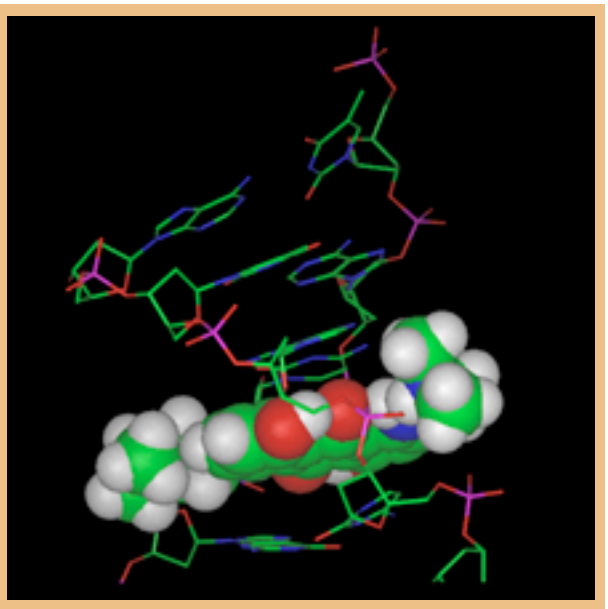
- support the NC3Rs and other funders in delivering high quality programmes to develop engagement, uptake and understanding of 3Rs approaches;
- facilitate resource and data sharing and collaboration across industry and academia;
- ensure the 3Rs are at the heart of all relevant science including the training of research leaders of the future;
- enhance the role of Home Office inspectors in disseminating 3Rs advances;
- enable our targeting of the more severe procedures through recording ‘actual severity’; and
- more generally, improve awareness and understanding about why animals need to be used in research.



Box 5: The NC3Rs in action

Research: The NC3Rs[1] has invested £35.1 million for research to support advances in the 3Rs across the biosciences. Over half of this is for research to replace animal use. NC3Rs-funded researchers have provided opportunities to minimise animal use in areas such as cancer, epilepsy and multiple sclerosis research and toxicity testing. This involves using the latest technologies including tissue engineering, microfluidics and mathematical modelling. In 2011, the Centre launched the first challenge-led research competition, CRACK IT Challenges, which is designed to support economic growth and the commercialisation of 3Rs technologies by bringing together scientists from universities, small and medium-sized enterprises and major industries to tackle problems which if solved have 3Rs and business benefits.

Collaborations: The NC3Rs works collaboratively with over 30 companies in the pharmaceutical, biotechnology, chemical, agrochemical and consumer product sectors, nationally and internationally. This has resulted in changes to international regulations, for example, the removal of the requirement to do single dose acute toxicity testing in animals. The



Anti-cancer drug binding to DNA.

Credit PJ Smith, L Patterson & P Teesdale-Smith, Wellcome Images

Centre also works collaboratively with international regulatory agencies. This includes two initiatives jointly led by the NC3Rs and MHRA on reducing the use of 'recovery' animals in pharmaceutical development and using human tissue instead of animals for safety pharmacology studies.

1 http://www.nc3rs.org.uk/

2.1.1. Support the NC3Rs and other funders in delivering high quality programmes to develop engagement, uptake and understanding of 3Rs approaches

The research programme funded by NC3Rs has already delivered remarkable advances in alternatives as evidenced by reviews of the research portfolio and strategic awards (see Box 5). A range of further NC3Rs led initiatives are described in this Plan, including innovative approaches such as the CRACK IT Challenges competition which brings the brain power of academics and industry together to identify problems and find innovative solutions which promote the 3Rs. A new initiative in 2014 will be the launch of an online resource for scientists to improve their understanding of good experimental design.

The Government recognises that its funding for alternatives to research is a very small proportion of the overall funding it provides to the Research Councils which also fund animal experiments. However, it has demonstrated its commitment to the NC3Rs by increasing funding at a time when the fiscal consolidation has required substantial funding cuts to many other areas of government. In 2010/11 the NC3Rs received £5.3 million from government (MRC, BBSRC, Home Office) and this will increase to just over £8 million in 2014/15 (MRC, BBSRC, EPSRC, Home Office, Defra).

Other funders and agencies commissioning or carrying out research in animals also have a role to play in supporting 3Rs research. For example, BBSRC, working with the NC3Rs, has highlighted a call for

proposals on animal welfare measures and assessment (Action 1.9). Sixteen projects have been funded and BBSRC is planning a series of events to disseminate results throughout the course of the programme.

Funders now routinely use online tools to capture the outputs of the research they fund. This gives researchers an opportunity to show the benefits and impacts of their research such as publications, collaborations, patents and industrial funding. The Research Councils have undertaken to add to these tools to capture data not only on implementation of the 3Rs in research but also to allow researchers to report 3Rs impacts of their research (Action 1.7). Over time, such measures will act as a powerful means to change behaviour and culture, even further encouraging researchers to consider the 3Rs in the work they do. This will also provide an additional resource for understanding the extent of 3Rs innovation in research.

Relevant funding peer review processes include an assessment of the justification for animal use and an assessment of whether the numbers of animals proposed will provide robust experimental results. The Research Councils, working with the NC3Rs, are currently reviewing, updating and harmonising their requirements for this justification. This is with the aim of ensuring that every research programme and project proposal receives effective scrutiny before it is funded and that opportunities to implement scientific advances to replace, reduce or refine animal use are not being missed (Action 1.8).

The Technology Strategy Board (TSB) considers new pipeline technologies as part of its Emerging Technologies and Industries Strategy. Following a series of workshops held jointly in 2013 with the NC3Rs, TSB has selected “non-animal technologies” for feasibility study competitions opening in first quarter 2014 (Action 1.12). This demonstrates the real potential for technological development in this area in the UK.

2.1.2 Encourage government departments and agencies to place the 3Rs at the heart of their work

Many government departments and agencies have responsibility for research involving animals. We consider the role of regulators in Section 2.1.5. In this section we consider those who commission or perform such research and play an important role in promoting the 3Rs.

Defra has a number of agencies performing research to address the department’s responsibilities for animal (and human) health and environmental safety.

For example, the Centre for Environment, Fisheries & Aquaculture Science (Cefas) has moved away from death as an end-point in fish research, has developed protocols to reduce the number of fish used in routine testing across Europe, is actively researching methods to enhance fish welfare and was the first laboratory in Europe to completely eradicate the use of mice in testing the safety of shellfish (in collaboration with the Food Standards Agency and the Home Office – see Box 6). It is also notable that a large number of fish are immobilised simply for tagging. This has been counted as a procedure in the Home Office annual statistics although the tagged fish continue to function, swim and migrate normally.

The Animal Health & Veterinary Laboratories Agency (AHVLA) has made great strides over the years in the use of non-animal alternatives and in refining end-points where animals must be used. Some of the reductions involve areas for which there is a statutory responsibility such as diagnostic tests for avian flu and rabies. Co-ordinated effort across Europe also reduces

Box 6. How government departments, agencies and public bodies are promoting the 3Rs in their work

- The detection of paralytic and diarrhetic toxins in commercially harvested shellfish has traditionally used severe bioassays in mice involving significant suffering. A collaborative effort between Defra (Cefas), FSA and Home Office (ASRU) inspectors has led to the successful optimisation and implementation of two non-animal alternative tests. Over 8,000 mice were used in 2007. In 2012, fewer than 50 mice were used in the traditional animal test compared with a projected 13,000 mice which would otherwise have been needed to ensure human safety. The animal assays were fully replaced in May 2012 and animals are no longer used for shellfish safety testing. The alternative tests are now being adopted more widely across Europe.
- Where a new vertebrate animal test is required for the assessment of the potential reproductive toxicity of an industrial chemical (e.g. to assess its possible impact on fertility), the traditional "gold standard" test involves the study of rats over two generations, as described in OECD Test Guideline 416[1]. A new test has been developed – the Extended One

Generation Reproductive Toxicity Study (EOGRTS), which offers a much more flexible study design that can generate sufficient information for regulatory purposes without the mandatory production of the second generation. The EOGRTS uses about half the number of animals (reducing from 2,600 to 1,400 per test) compared with the two-generation study. The EOGRTS was adopted by the OECD in 2009. Subsequently, Defra and the HSE (the UK Competent Authority for REACH), along with authorities from other key Member States, have successfully promoted its adoption in the EU. Adoption of the EOGRTS in the REACH Test Methods Regulation is now anticipated in mid 2014.

1 http://www.oecd.org/env/ehs/testing/

the potential for duplication (e.g. recently in researching Schmallenberg virus) although this may often increase the number of animals used in the UK on behalf of Europe.

The Food & Environment Research Agency (Fera) carries out much of its work using wild animals and carefully reviews all research proposals to ensure the principles of the 3Rs are being effectively applied. Fera also works with the Universities Federation for Animal Welfare (UFAW) and the RSPCA to provide expert training and guidance for those wishing to work with wild mammals or birds to ensure best practice at all times.

Other examples of government departments applying the 3Rs include Public Health England (PHE) which

has recognised that the detection, tracking and management of outbreaks of disease is an area where innovation using whole genome sequencing of pathogens can replace the use of techniques which have previously required generating antibodies in rabbits (Action 1.11). An initiative is underway to explore this further with the potential to significantly reduce the use of animals in this area.

In fact all government departments, agencies and public bodies which commission research which involves the use of animals, or which are responsible for regulations which require animal testing, have a duty to consider the 3Rs in their work (Action 1.13) along with supporting others in setting out clearly the benefits the research can bring and helping to improve understanding and awareness of the issue.

2.1.3 Facilitate data sharing and collaboration across industry and academia

The MRC and BBSRC are the major public funders of animal research in the academic sector and have a key role to play in influencing the culture of researchers who use animals and in providing incentives for researchers to engage with the 3Rs.

Working with the NC3Rs, Research Councils are looking for ways to increase resource sharing (Action 1.2) so that individual research programmes can make the most of available resources. These may be outcomes of research, animals, data or other resources. This will enable researchers to make the most of available information and will help to prevent duplication and increase collective knowledge and experience in specific areas of research. It will also provide greater efficiencies in research as well as encouraging cross-disciplinary collaboration.

The UK makes a major contribution to global mouse phenotyping and the free exchange of information about genetically altered strains. This is achieved through programmes such as the International Mouse Phenotyping Consortium (IMPC) and the Knockout Mouse Program (KOMP2) and means that duplication of work which would otherwise involve much greater numbers of animals is avoided (Action 1.2).

2.1.4 Ensure the 3Rs are at the heart of all relevant science including the training of research leaders of the future

To ensure the 3Rs are at the heart of animal-based science, the Research Councils are issuing updated requirements for all funding applications which involve the use of animals. This is to ensure that every research proposal receives effective scrutiny before it is funded and that opportunities to implement 3Rs advances are not missed. Furthermore, a strategy to embed the 3Rs in the training and development of scientists from the start of their careers is driven through the NC3Rs-funded PhD studentship scheme (Action 1.3).

2.1.5 Enhance the role of Home Office inspectors and other regulators in disseminating 3Rs advances within a robust regulatory framework

As regulators of animal research, the Home Office Animals in Science Regulation Unit (ASRU) plays a central role in dissemination of best practice. The 2012 amendments to the Animals (Scientific Procedures) Act (ASPA), implemented by the Government to transpose the new Directive (2010/63/EU), have promotion of the 3Rs at their core. Home Office inspectors, in reviewing applications for projects, encourage and require 3Rs approaches to be robustly implemented

Box 7. Refinement opportunities in batch testing of biologicals

- Assessing the safety and efficacy of each batch of Botulinum toxin involves a very severe test in mice in which animals become paralysed and will die if not humanely killed. One manufacturer has validated an alternative test to replace at least some of the animal use for their particular product. The Home Office and MHRA are actively pressing other manufacturers to do likewise. Given this may take some time to complete, Home Office inspectors have meanwhile required refinement of the mouse test to reduce the severity as far as possible. For example, mice are checked very regularly, at least once every hour, throughout the day and night to ensure they are observed as soon as they show clinical signs and humanely killed whenever possible. Collaboration such as this between the Home Office, MHRA, manufacturers and their testing laboratories is very important. We are also engaging with the European Commission and internationally (e.g. with US FDA) to share best practice more widely.
- Since 2007, a similar approach taken by VMD has led to a 50% decrease in the number of animals used per batch in testing the safety and efficacy of clostridial vaccines intended for use in horses.

(see Box 7). In this, they are particularly effective in relation to refinement and reduction. However, given the complexity of science, access to sound reference material regarding replacement options is not always readily available.

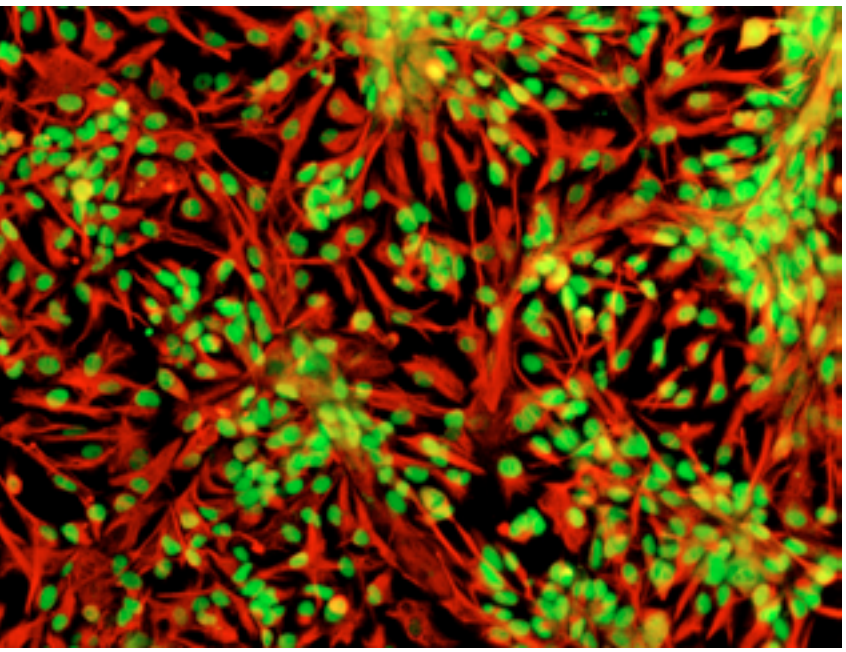
A number of approaches are being pursued to address this, including greater emphasis in the relevant Guidance on the Operation of the Act. Applicants are left in no doubt about their absolute responsibility to ensure they have rigorously explored all options to implement the 3Rs in their application. Means of more effectively acquiring and disseminating information, particularly on replacement options, are also being explored (Action 1.4).

The EU Directive provides an opportunity to require companies in the UK to take positive action to develop and validate alternative tests, particularly in relation to batch testing of biological products such as vaccines and toxins with significant benefits to human health for example. In relation to novel products, both MHRA in relation to human health and VMD in relation to animal health are robustly pursuing this by requiring applicants for new Marketing Authorisations to demonstrate the absence of a suitable non-animal release test before an authorisation based on an animal test will be approved. Further, with existing biological products where a non-animal test is known to have been validated and accepted for one manufacturer's product, we will pursue other manufacturers to validate a non-animal test for their similar product. This includes waiving the fees normally charged for varying a Marketing Authorisation where the change represents implementation of the 3Rs.

The VMD is in the final stages of completing a project which has involved reviewing all veterinary vaccines produced in the UK to identify where animals are still being used for batch release and whether any tests are unnecessary. As a result of these measures, it is estimated that about 5,000 fewer animals will be used each year in testing for an equivalent number of batches released.

Where veterinary medicines are used in food-producing animals it is important to establish potential harmful effects in humans who may consume the meat, milk, eggs, etc. and also to understand how the medicines are metabolised and depleted from the animal tissues so that safe withdrawal periods can be set. This requires the use of animals, mainly target species, but by implementing 3Rs approaches we ensure the numbers involved are minimised.

Nevertheless, it is accepted that biological products vary significantly according to the production process



Human neural stem cells.
Credit Yirui Sun, Wellcome Images

and read across from one to another cannot be assumed. Further, where the product tested in this country is destined for global markets, we realise that the Marketing Authorisation in each of those countries needs to be amended before the animal test becomes redundant.

This is a significant problem which risks exporting tests, many of which are severe, to overseas countries where welfare standards may be lower. We are actively pursuing this dilemma with the European Commission to seek a way forward which does not simply export the problem elsewhere.

2.1.6 Enable our targeting of the more severe procedures through recording 'actual severity'

We are committed to implementing a robust system of reporting actual severity of procedures on animals from January 2014. To ensure the data collected are as reliable as possible, Home Office inspectors have conducted a pilot study during 2013 which will form the basis of guidance on categorising actual severity as sub-threshold, mild, moderate or severe. These data will provide clarity on the burden of harm, including cumulative harm, to animals used in research and, over time, will measure the effectiveness of refinement efforts, particularly for those procedures at the most severe end of the spectrum (Actions 1.5 and 1.6).

2.2 Influencing the uptake and adoption of 3Rs approaches globally

Animal experimentation in the UK constitutes only a relatively small proportion of global use of animals in research and we want to share some of the benefits of the progress we have made in the UK. Furthermore, much regulatory testing involving animals will only be replaced with non-animal techniques when the latter is accepted globally (see Section1, Challenges to delivery).

The Government is therefore committed to spread best practice and use its influence overseas to work with other countries and international regulators to replace, reduce, and refine the use of animals, particularly in regulatory testing and also to improve understanding about why animals are used in research. This will benefit the UK economy as well as enhance animal welfare.

Our key objectives are to:

- support the NC3Rs' international initiatives;
- engage with other countries, especially through ICH and OECD, to promote the harmonisation of global regulatory standards which use alternatives wherever possible;
- provide an evidence base for where changes would be beneficial to international regulations which require animal use; and
- work to end unnecessary animal testing for cosmetics globally.

Through this programme, we will further develop the UK's position in influencing the international uptake of 3Rs approaches and provide an opportunity to contribute to a more harmonised global framework for the benefit of animal welfare and UK competitiveness. The programme will:

- enable companies with high ethical standards to trade in growing markets that currently require the use of questionable animal tests in order to market their products; and
- help support the UK's Life Sciences industry, an important component of the Government's Industrial Strategy, by harmonising international regulatory testing requirements.

In Table 2 we describe the actions we will be taking in this international programme.

2.2.1 Supporting the NC3Rs' international initiatives

The NC3Rs is working to ensure the international adoption of best practice in a variety of areas. These include:

- reducing the use of animals in safety pharmacology studies by using human tissues, working with 25 pharmaceutical companies, contract research organisations, academics and regulators from the UK, Europe and the USA;
- minimising the use of recovery animals (rats, dogs or non-human primates) in pharmaceutical development; and
- refining inhalation toxicology methods to make the 'fixed concentration procedure' more widely adopted through objective scoring.

2.2.2 Engage with other countries, especially through ICH and OECD, to promote the harmonisation of global regulatory standards which use alternatives wherever possible

The work at an international level presents an opportunity to contribute to a more harmonised global framework for the benefit of UK competitiveness alongside demonstrating the UK's commitment to reducing the use of animals in research and providing global leadership. This is a key issue for the UK and the Life Sciences sector and is an important component of the Government's Industrial Strategy[14]. Action is geared towards supporting and encouraging economic growth.

Harmonisation of international regulatory requirements and the adoption of better alternatives will support this. The UK must ensure that it enters international negotiations in good faith with the intention of accepting the outcome if at all possible, to maintain credibility and commitment to reduce gold plating.

Box 8. An example of overseas engagement – China

Working with FCO colleagues, we will support a Chinese initiative to develop standards for research animal welfare and ethical use. Through funding an international seminar on this topic, we will help drive the endorsement of these standards as national regulations. Building on this collaboration, we will further work with Chinese regulators (e.g. CFDA) to develop a science-led strategy and action plan to cease unnecessary animal testing of cosmetics and to harmonise safety testing of medicines in animals (Actions 2.4 and 2.5).

14 The Government is developing long-term strategic partnerships with industry sectors where we can have the most impact on growth.

With increasing globalisation of both commerce and science comes a need for greater harmonisation of approaches. Actions 2.1 to 2.5 are designed to address these through a number of approaches. For example, the work of the NC3Rs together with the MHRA (Action 2.1) will help to solve specific problems in regulatory science and are already providing a focus for collaboration in these issues amongst global industries.

The UK can also use its global standing both as a leader in the development and implementation of the 3Rs and as a nation at the forefront of innovation in this area to influence international regulators to early adoption of scientifically proven 3Rs alternatives for regulatory testing. Actions in 2.3 set out just a few examples that we are working on at present.

2.2.3 Working to end unnecessary animal testing for cosmetics globally

Testing of cosmetics on animals is an area of great public concern (Action 2.4). In the UK, the testing of cosmetics in animals has not been permitted since 1998. Work is underway to develop an international strategy towards the eventual eradication of unnecessary animal testing of cosmetics products, adopting a science-led approach.

The European Union, via the seventh amendment to the Cosmetics Directive, brought in a phased approach to banning animal testing. Initially, a ban on the testing of finished cosmetics in animals was implemented in 2004. This was followed by a ban on the testing of ingredients or combinations of ingredients in 2009 together with a partial marketing ban which applied to all except tests for the most complex human health effects (e.g. carcinogenicity tests) where alternatives were not available. The marketing ban was completed in 2013.

There may remain a requirement for some animal test data to demonstrate safety of cosmetic ingredients in the absence of validated alternative tests. But in most cases historic animal test data, or data from tests undertaken for non-cosmetic purposes, can be used to assure safety.

This compares with other markets across the globe which may either require animal testing (e.g. China) or may accept data from animal testing as evidence of human safety (e.g. USA). Hence, animal tests are either explicit or implicit in the legislation.

Ethical manufacturers within the European cosmetics industry believe that animal tests on finished cosmetics are unnecessary because safety can be definitively demonstrated by other means. Making use of connections offered through the Foreign & Commonwealth Office (FCO), we propose to engage with the relevant overseas regulators and scientists to promote strategies which will enable and encourage them to move away from unnecessary animal testing.

We believe this has potential benefit for all concerned. For example, our proposed initiative in China (Action 2.5 and Box 8) will not only open up this market for UK and European companies but will also open up UK and European markets to Chinese companies. At the end of

the day, consumers will benefit from a diverse range of safe cosmetics which have not undergone unnecessary animal testing.

2.3 Promoting an understanding and awareness about the use of animals where no alternatives exist

We are committed to a culture of openness and transparency to help improve public understanding of the research which is carried out as well as the many ways in which alternatives are used. Also to explain some of the real public and animal health benefits that have resulted from the research which has been carried out on animals.

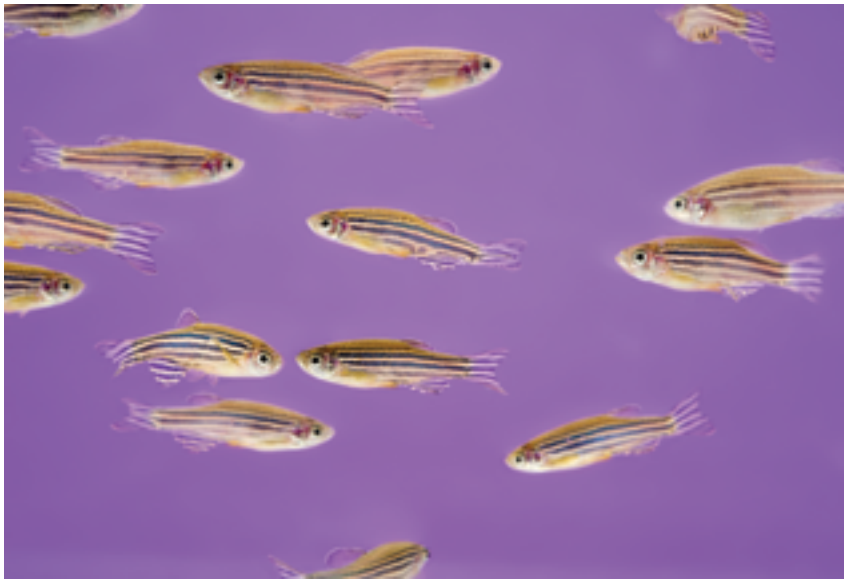
Openness is crucial to ensure that we signal to global industry and academia that we are a great destination for high quality life sciences research. We will promote that research in an environment which both supports openness about the need for the use of animals and the benefits that can result, e.g. from cholesterol lowering drugs to rabies vaccines for family pets, but which also nurtures a culture of innovation to look for new and improved ways of tackling 3Rs questions.

We believe the research community and the public will benefit from knowing more about the actual severity, in terms of pain or distress, experienced by research animals and may have fears or misconceptions allayed. We therefore welcome the new European requirement to record, at the end of each procedure, the category (sub-threshold, mild, moderate or severe) of severity actually experienced by each animal. During 2013 we have conducted pilot record collection to ensure the quality of reporting is as accurate and consistent as possible and we will publish guidance. Not only will actual severity reporting provide greater transparency it will also enable us to identify where the greatest severity occurs and to focus refinement initiatives towards those procedures (Action 3.2).

We have welcomed the work that a coalition of industry, academia, health charities and research funding bodies is leading on a Concordat on Openness[15], about animal research. This initiative also aims to improve understanding and awareness about the ways in which animals are used in scientific, medical and veterinary research in the UK (Action 3.3).

The Home Office is delivering on its commitment to review section 24 of ASPA, the so-called ‘Confidentiality Clause’. Multi-stakeholder workshops are being held to seek ideas of how the licensing process can be made more open and transparent. At the same time, personal safety must be assured by safeguarding identities of people and places, and intellectual property must be protected to ensure that scientists’ greatest assets, their ideas, are not plagiarised. This is a complex piece of policy being developed as part of delivering this Coalition Commitment (Action 3.4).

Through all these initiatives, we want to improve public understanding of the context of animal research and the licensing framework and to engage the public and the research sector in a transparent conversation around the use of animals in research. A mechanism for gauging the success of all these and other approaches will be monitored through the public response to surveys such as Public Attitudes Survey 2014 (Action 3.1).



15 http://www.understandinganimalresearch.org.uk/policy/concordat-on-openness-on-animal-research

Section 3
Tables

In Section 2 of our Delivery Plan we have described a wide range of measures to promote the 3Rs, both within the UK and internationally and provide opportunities for researchers and industry to address the 3Rs in their work. The actions include encouraging existing programmes and fostering new, specifically targeted, programmes.

In this section we describe each of the actions in greater detail in a series of three tables. Each table considers delivery against one of our three strategic priorities, putting the 3Rs at the heart of a science-led programme:

- Strategic Priority 1 – a domestic programme which focuses on advancing the use of the 3Rs within the UK;
- Strategic Priority 2 – an international programme aimed at influencing the uptake and adoption of 3Rs approaches globally; and
- Strategic Priority 3 – a programme aimed at promoting an understanding and awareness about the use of animals where no alternatives exist.

In each table, we consider specific actions which are either underway or proposed. We indicate the lead organisations for each action, and provide some key milestones against which success will be measured. Finally, we indicate our expected timelines for each of the milestones or, where appropriate, we indicate where work is ongoing.

We will review our progress against these milestones a year after publication of this Delivery Plan.

Strategic Priority 1: Advancing the use of the 3Rs by putting them at the heart of science-led programmes

Title/lead organisation(s)	Actions (underway or proposed)	Measures of success and key milestones	Timelines
1.1 National Centre for the Replacement, Refinement and Reduction of Animals in Research programmes (NC3Rs)	1) Publication of the second review of the NC3Rs research portfolio by November 2013.	- Received positively by stakeholders and sector. - Enhanced understanding by stakeholders and public of high quality research funded by the NC3Rs and the animal welfare, scientific and societal benefits of this.	Published November 2013.
	2) Launch of the NC3Rs Experimental Design Assistant online resource.	Early uptake and use by research community and improved understanding of the 3Rs benefits to good experimental design.	Spring 2014.
	3) CRACK IT: The 2013 CRACK IT Challenges competition consists of five Challenges identified jointly by the NC3Rs and industry sponsors who provide in-kind contributions including data, access to compounds, validation studies, etc. CRACK IT Challenges is a milestone-driven funding competition from the NC3Rs which is designed to (i) minimise the use of animals in research; and (ii) support the development of marketable products and/or improved business processes. The total budget for the 2013 round of CRACK IT Challenges is approximately £7M.	Contracts awarded to address the challenges.	The winners of the competition will be announced in January 2014.
	4) Strategic award: Imaging technology development for the 3Rs – the NC3Rs have recently announced a strategic funding call to support high-quality research proposals to address genuine technological challenges in preclinical imaging which if solved would advance science and the 3Rs. The total budget for this strategic call is £1M.	Awards made.	Successful applicants will be announced in March 2014.
	5) Disease models – the NC3Rs are developing a programme of work, based on previous experience, focusing on disease models and efficacy testing. This includes disease areas such as asthma, epilepsy and pain, and they are working with the ABPI to secure funding to lead on this. An initial priority is cancer models.	Engaging and building relationships with the cancer research community in applying the 3Rs to their research.	Workshop to bring the cancer research community together – Spring 2014.
1.2 Improved resource sharing including outcomes of research, resources, animals and data (NC3Rs with MRC and BBSRC)	Examples of ongoing work include: - Recently launched NC3Rs infrastructure for Impact (IfI) scheme. - Shared Ageing Research Models (ShARM – Biorepository of aged mouse tissues) - Availability of Non Human Primate tissue from Centre for Macaques (CFM). - Enhanced archiving of animal models in academia. - Coordinated mouse phenotyping of genetically altered animals (IMPC). - The NC3Rs and funders are considering ways to enhance data sharing and publication of negative results.	Four Infrastructure for Impact projects awarded totalling £1.3M.	Ongoing.

Title/lead organisation(s)	Actions (underway or proposed)	Measures of success and key milestones	Timelines
1.3 Postgraduate 3Rs training (NC3Rs)	PhD studentship scheme as part of the NC3Rs strategy to embed the 3Rs in the training and development of scientists from the start of their careers. To date 37 awards in total have been made.	Improved training on project design for PhD students.	Ongoing.
1.4 Increase the impact of Home Office inspectors and other regulators in the dissemination of 3Rs advances and advise about implementation (HO and MHRA)	Enhanced dissemination of the 3Rs through continued development of expert knowledge networks (internal HO Inspectorate activities working with others e.g. NC3Rs) and externally with licensees through: - publication of Guidance on the operation of the Act with increased emphasis on 3Rs and harm-benefit assessment; - outreach activities attending and speaking at meetings and conferences; and - regular discussions with new and existing licensees.	i) Guidance to new regulations published including significant material on 3Rs and harm-benefit assessment. ii) Inspectorate have formalised a strategy for internal knowledge transfer. iii) Inspectorate have formalised a strategy for dissemination of 3Rs information and implementation with licensees. iv) Continuation of Continuous Professional Development activities and networking with relevant stakeholders.	i) December 2013. ii) July 2014. iii) July 2014. iv) Ongoing.
	Increased requirement to applicants for new Marketing Authorisations to demonstrate absence of a suitable non-animal test before an authorisation based on an animal test will be approved. Working with the Home Office, MHRA to pursue manufacturers with existing Marketing Authorisations to validate non-animal tests for their product, particularly where the animal test is severe, or where another manufacturer of a similar product has validated a non-animal test.	i) New Marketing Authorisations based on non-animal tests being approved. ii)Waiving of application fee by classifying such a change as a Type 1 variation to the Marketing Authorisation. iii) Non-animal tests for existing Marketing Authorisations being submitted.	Commenced in earnest in 2010 and on-going.

Title/lead organisation(s)	Actions (underway or proposed)	Measures of success and key milestones	Timelines
1.5 Refinement of models (RSPCA with HO)	Work to refine the most severe models to avoid or reduce animal suffering. Models to be considered include: - Experimental Autoimmune Encephalomyelitis (EAE); - Seizures; - Rheumatoid arthritis; and - Sepsis.	- Reports on each of the selected topics prepared and published. - Recommendations promulgated.	i) EAE report published late 2012. ii) Seizures report published 2013. iii) Rhematoid arthritis report to be published early 2014. iv) Sepsis models report to be published Spring 2014. v) Inspectors report active implementation by licence applicants.
(Cefas with NC3Rs)	i) Measures taken to eliminate death as an endpoint in fish disease studies to reduce suffering. This represents between 76% and 94% of the fish work of the National Reference Laboratory. ii) Refinement of the Fish Sexual Development Test (FSDT) for detecting early life-stage effects and potential adverse consequences of putative endocrine disrupting compounds on sexual development (Cefas - funding from NC3Rs). The development of molecular markers for stickleback endocrine function and protocols for studying behaviour of the animals to facilitate a decrease in use of sticklebacks iii) NC3Rs funding to examine indicators of fish wellbeing.	i) Active evaluation of different ways to reduce animal suffering and animal numbers used. The new project licence for this work does not include death as an end-point. ii) Has resulted in a 25% to 50% reduction in the number of fish needed for this test. A calculation of the number of chemicals requiring FSDT testing in Europe alone shows that use of sticklebacks in this test will result in about 90,000 fewer fish being sacrificed. iii) Project report demonstrating better fish welfare in experimental systems, but also more widely in farmed fish in aquaculture.	i) New licence already issued; refinement work ongoing. ii) Already achieved reduction; further improvement ongoing. iii) Ongoing. Report in 2015.
1.6 "Actual Severity" Reporting in Annual Statistics on Use of Animals in Science (HO)	Implement retrospective reporting of the "Actual Severity" of all scientific procedureson protected animals in line with the Directive (2010/63/EU). This will enable us to better understand: - levels of overall animal suffering in terms of numbers of animals experiencing each category of severity – sub-threshold, mild, moderate or severe; - which procedures are most severe and in which species; and - whether 3Rs implementation is having an impact on reducing overall severity.	i) Completion and review of pilot trial for retrospective (actual) severity reporting. ii) Development of Guidance on recording Actual Severity. iii) Commence project to map phenotyping of GA mouse strains to actual severity categories commenced (with external stakeholders e.g. MRC Harwell). iv) Completion of analysis of pilot data for limited publication. v) Publication of first complete year of retrospective actual severity data. vi) Provision of complete year data to the EU Commission.	i) December 2013. ii) January 2014. iii) March 2014. iv) July 2014. v) July 2015. vi) By November 2015.

Title/lead organisation(s)	Actions (underway or proposed)	Measures of success and key milestones	Timelines
1.7 Capture of information on scientific outputs relevant to 3Rs and the implementation of 3Rs advances (MRC and BBSRC)	Research Councils to improve the capture of information on scientific outputs relevant to 3Rs and the implementation of 3Rs advances in funded projects. Data on 3Rs implementation and relevant outputs captured via the introduction of new questions in the Research Councils' computerised data gathering systems. Encouragement of other charitable funders to do likewise.	i) Successful collection of captured data. ii) Publication of analysis of data collected. iii) Other major charitable funders of animal research able to collect comparable data.	i) First data collected autumn 2014. ii) First analysis published summer 2015. iii) Ongoing.
1.8 Updated requirements for applications which include animal research (MRC and BBSRC)	Research Councils to issue updated requirements and guidance for applications which include research involving the use of animals. Ensure that every research programme and project proposal receives effective scrutiny before it is funded and that opportunities to implement scientific advances to replace, reduce or refine animal use are not missed.	i) Drafting and issuing of new guidance. ii) Evaluation of impact of new guidance.	i) New guidance in place by Jan 2014. ii) Evaluate the effect in the autumn of 2014.
1.9 Highlight on 'Animal Welfare: Measures and assessment' (BBSRC and NC3Rs)	Dissemination event: BBSRC joint highlight with NC3Rs on 'Animal Welfare: Measures and assessment'. 16 projects funded totalling nearly £5.8M.	BBSRC working with NC3Rs to ensure that outputs are captured and disseminated to ensure better monitoring and assessment of welfare in the future. Dissemination events during the course of the programme.	i) Networking workshop for grant holders Autumn 2013. ii) Further dissemination events planned with one agreed for Spring 2015.
1.10 Veterinary vaccine testing (VMD and Defra)	Review of batch testing of biologicals such as veterinary vaccines. Identification of areas for possible replacement in the batch testing of vaccines, especially areas of such testing involving animals where the replacement of the test would have the biggest impact in reducing number of animals used.	A report setting out the number of animals used during in-process and final product testing of batches of vaccines released by the VMD.	Report published 2014.
1.11 Human Vaccine testing (PHE).	Development of 3Rs techniques for use in human vaccine development. i) Working with academic and clinical partners to develop a BCG model that allows assessment of efficacy of novel TB vaccines which refine the use of animal models. ii) Actively developing cell-based assays for the characterisation of the manufacturing process and the batch release of the product, evaluating the potential to replace toxicity release tests.	i) This model has the potential to refine the current test to allow further development to take place at human clinical trials stage. ii) If developed, the Toxin Neutralisation Assay test will replace the current potency test resulting in a reduction in the numbers of animals used and the severity of the testing.	i) Ongoing. ii) Ongoing.

Title/lead organisation(s)	Actions (underway or proposed)	Measures of success and key milestones	Timelines
1.12 Development of non-animal technologies (TSB and NC3Rs)	Technology Strategy Board (TSB) development of non-animal technologies. Competition to fund early stage feasibility studies investigating novel non-animal technologies to improve product development across a range of industries. Up to £4 million funding available.	Industry and sector infomed of competition in autumn 2013 and awards made in 2014. Output from the funded studies will be novel non-animal technologies that produce approaches that are 'fit for purpose'.	i) Competition opens February 2014, closes April 2014. ii) Funded studies to begin 2014.
1.13 Ensure government departments and agencies consider the 3Rs when commissioning or funding research involving animals (GCS and CSAs)	Government Chief Scientist and Departmental Chief Scientific Advisers (CSAs) to ensure that government departments and agencies consider the 3Rs when commissioning or funding research involving animals. Commitment from departments and their agencies on the 3Rs including policy statements overseen by the CSAs.	i) All government departments including DH, MoD, Defra, HO, BIS and agencies have statements on their websites.	i) Ongoing.
1.14 "Minimisation of animal testing" leaflet (Defra and HSE)	As UK Competent Authority for REACH, Defra and HSE already produce a leaflet entitled "Minimisation of animal testing". This is a popular publication and provides a brief summary of the opportunities that are available to REACH registrants to minimise the amount of animal testing needed to comply with REACH registration. This initiative will ensure new information about advances in *in vitro* testing, particularly of irritants, is communicated to UK-based duty holders.	i) Update the publication "Minimisation of animal testing" which is popular and effective in promoting the 3Rs in this area. ii) Encourage the European Chemicals Agency (ECHA) to similarly update its guidance in this area for those with registration duties in 2018.	i) Publish by end of 2014. ii) During 2014.

Strategic Priority 2 – Influencing the uptake and adoption of 3Rs approaches globally

Title/ lead organisation(s)	Actions (underway or proposed)	Measures of success and key milestones	Timelines
2.1 NC3Rs international science-led programmes **2.1.1 Human tissues and pharmaceutical development programmes** **(NC3Rs and MHRA)**	**NC3Rs/MHRA joint working group on human tissue for safety pharmacology** – Joint working group to generate an evidence base to support the use of human tissue to reduce animals in safety pharmacology studies. The group consists of 25 pharmaceutical companies, contract research organisations, academics and regulators from the UK, Europe and USA. This forms the basis of a wider programme of work on the use of human tissue for basic and applied research, including in the areas of asthma and pain.	An evidence base is developed to support the use of human tissue to reduce the use of animals in safety pharmacology studies.	The initial output of the working group will be reported in spring 2014.
	NC3Rs/MHRA joint working group on recovery animals in pharmaceutical development – Joint working group to consider potential opportunities for minimising the use of recovery animals (rats, dogs or non-human primates) in pharmaceutical development. The group consists of 32 pharmaceutical companies, contract research organisations and regulators from the UK, Europe and USA, including the FDA.	Potential opportunities are identified to minimise the use of recovery animals in pharmaceutical studies.	The initial output of the working group will be reported in spring 2014.
2.1.2 Chemical safety programme **(NC3Rs, HSE and PHE)**	**NC3Rs working group on the fixed concentration procedure (chemical safety)** – This working group supports the international adoption of the fixed concentration procedure (FCP) for acute inhalation toxicity testing. The NC3Rs is working with inhalation toxicity experts from contract research organisations, academia, and other government bodies, to make the FCP more objective to encourage wider adoption of the approach across OECD Member States.	Objective scoring system to encourage wider adoption of FCP across OECD member states.	The output of this work will be published in spring 2014.

Title/ lead organisation(s)	Actions (underway or proposed)	Measures of success and key milestones	Timelines
2.2 Review of OECD Test Guidelines **2.2.1 Systematic review of OECD Test Guidelines to address 3Rs** **(Defra and PHE)**	Systematic review of Organisation for Economic Co-operation and Development (OECD) Test Guidelines (TGs) to address 3Rs. In liaison with industry partners as well as regulatory authorities, we will review TGs where a potential to replace, reduce or refine animal studies is identified. Current work is on skin and eye sensitisation and irritation (see also Action 1.14). Proposed additional work is on the acute dermal toxicity. All are areas where the a review of the protocols would not only address 3Rs but provide an advance in science.	i) Adoption of TG under review TG430 and TG431 – Skin irritation and corrosion. ii) Submit proposal to OECD for review of the use of both genders in the acute dermal toxicity assay (TG402). iii) Commence review of data for the use of both genders in the acute dermal toxicity assay (TG402).	i) April 2014. ii) January 2014. iii) June 2014.
2.2.2 Reproductive toxicology (EOGRTS) **(Defra and HSE)**	The Extended One-Generation Reproductive Toxicity Study (EOGRTS) offers a much more flexible study design than the traditional two-generation approach (OECD TG416). The EOGRTS has been shown to generate sufficient information for regulatory purposes without the mandatory production of a second generation. The EOGRTS uses about half the number of animals – reducing from 2,600 to 1,400 rats per test. It was adopted by the OECD into its test guidelines in 2009.	i) In association with competent authorities from other key EU Member States, to promote the adoption of the EOGRTS in the EU. ii) To complete the process by achieving adoption of the EOGRTS in the REACH Test Methods Regulation.	i) Ongoing. ii) Summer 2014.
2.3 Influence regulatory frameworks which require animal testing: **2.3.1. Adverse Outcome Pathways for chemicals** **(PHE and Defra)**	**Adverse Outcome Pathways** – International Development of New Approaches to Chemicals Testing. Historically, identifying adverse effects of chemicals has relied on using large numbers of animals to test their toxicity, one by one. If we could identify the chain of linked events from an initial chemical impact at the molecular level to responses at higher biological levels, we might be able to use *in vitro* techniques such as genomics to predict impacts up to the level of an organism or even populations. This would offer ways of reducing the need for tests using intact animals, as well as speeding up the assessment of chemicals. The concept of Adverse Outcome Pathways (AOPs) offers a mechanistic way to describe such a sequential chain of causally linked events. In 2012, the OECD launched a new programme to develop AOPs, in which the UK is collaborating. Appropriate AOPs to be validated and incorporated into OECD Test Methods toolkit as quickly as possible, via outputs of UK-funded research made available to the OECD programme.	Three relevant projects are underway: i) UK-Japan collaborative project – Critical review of key knowledge gaps to support AOPs for OECD test guidelines for aquatic organisms. Delivery of critical review of key knowledge gaps to support AOPs for OECD test guidelines for aquatic organisms delivered by UK and Japan. ii) Defra-funded project (Cranfield University) – In Silico Predictions of *In vivo* Toxicity: Are interspecies extrapolations off tangent. Final report published on accuracy of inter-species extrapolations of in silico predictions of *in vivo* toxicity. iii) Defra-funded project (Cefas, Universities of Birmingham and Liverpool) - The use of systems toxicology to re-construct molecular AOPs – can chemical mixture toxicity be predicted to aid environmental risk assessment and regulation? Final report published on the use of systems toxicology to re-construct molecular AOPs.	i) June 2014. ii) September 2014. iii) March 2015.

Title/ lead organisation(s)	Actions (underway or proposed)	Measures of success and key milestones	Timelines
2.3.2 Approaches for pharmaceuticals **(MHRA and VMD)**	**Harmonisation of approaches within regulatory frameworks:** - Harmonise approaches with respect to the 3Rs, and promote their uptake in pharmaceutical development. - Contribute to ongoing exploration of alternatives to using animals in testing of hazardous materials. Support the harmonisation of global regulatory standards. Unless all regulators accept an alternative to an animal test, the animal test would still be carried out by industry to ensure widespread marketing – essentially performing to the 'lowest common dominator' (and highest animal use) despite better and more economic tests being available. Continue to work with other regulatory agencies to interpret ICH and VICH flexibly, especially in light of emerging markets which are known to be less flexible. Continue to insist of adherence of OECD Good Laboratory Practice (GLP) requirements to avoid duplication of studies, especially important for emerging markets which are not party to the Mutual Acceptance of Data procedures. Provide a challenge to industry for already authorised projects and highlight where they are performing unnecessary animal testing and set out our expectations for change.	i) MHRA engaged at European and wider international levels with pharmaceutical regulators to promote the uptake of the 3Rs and harmonise approaches at all stages of pharmaceutical development. ii) MHRA encouraging the use of multiple end-points in one study to work to reduce the use of animals – an example would be including genotoxicity testing in animals in other toxicity studies. iii) VMD and MHRA influencing the development and revision of European Pharmacopoeia monographs such that, wherever feasible, testing in animals is replaced or removed or refined. (This creates a wider outreach than simply the EU as more countries are signed up to the pharmacopeia.) iv) VMD participating in the CXMP 3Rs group which is intended to identify and progress areas for regulatory change which can enable reduced testing in animals. v) VMD and MHRA actively challenging industry for already authorised projects and highlighting where they may be performing unnecessary animal testing. Setting out our expectations for change. vi) Defra project to review of accuracy of inter-species extrapolations of in silico predictions of *in vivo* toxicity.	i) Ongoing. ii) Ongoing. iii) Ongoing. iv) Ongoing. v) Ongoing. vi) September 2014 – final report published.

Title/ lead organisation(s)	Actions (underway or proposed)	Measures of success and key milestones	Timelines
2.3.3. Promote 3Rs in food safety regulation **(FSA and Cefas for Mouse bioassay replacement)** **(FSA for other opportunities)**	**3. Uptake of 3Rs and research / risk assessment to promote alternatives.** - Promote uptake of 3Rs in food safety regulation and support testing requirements in the UK and EU. - Promote and support research and risk assessment to underpin adoption of alternatives to animal-based testing for food safety where this can be done while maintaining an adequate level of consumer protection. Key opportunities exist in relation to: - To replace mouse bioassay in testing for shellfish biotoxins (i and ii). - To continue to encourage the European Commission and other Member States to consider the 3Rs principle when determining the need for animal studies in the risk assessment of GMOs (iii). - Engagement worldwide with food risk assessment and regulatory bodies to develop and harmonise approaches and to reflect these and the 3Rs in new or updated food regulations and testing requirements. Unless all regulators accept an alternative to an animal test, the animal test may still be carried out by industry to ensure widespread access to markets despite better and more economic tests being available (iv). - Considering the most appropriate means of generating data on approved food chemicals, including human studies where these are ethical and appropriate (v). - Clear guidance on the requirements for authorisation of novel foods and processes (vi).	i) Successful replacement of mouse bioassay in controls on shellfish toxins in UK. ii) Seek commitment from Commission to ensure other EU Member States replace mouse bioassay. iii) Key opportunities to influence include when the EU FP7 “GRACE” project comes to fruition, and when the Commission’s two-year feeding study with GM maize is completed. iv) FSA and its independent scientific advisory committees are engaged at EU and wider international levels, including strong engagement with the EFSA, the Commission, JECFA and Codex Alimentarius. v) An example is commissioning epidemiological studies to provide a basis for advice on caffeine intakes during pregnancy. vi) FSA provide clear guidance to industry on the requirements for applications for authorisation of novel foods and processes on where animal testing is and is not necessary for approval.	i) Completed. ii) During 2014. iii) During EU FP7 ‘GRACE’ project and two-year feeding study with GM maize. iv) Ongoing. v) Ongoing. vi) Ongoing.

Title/ lead organisation(s)	Actions (underway or proposed)	Measures of success and key milestones	Timelines
2.4 Cosmetics alternatives **(BIS and industry with support from HO and FCO – see also 2.5 below)**	- Work plan being developed to influence other non-EU countries in using alternatives to animal testing in bringing cosmetics to market (see also 2.5 below). - Access to data set on what third countries require as animal testing and what they require to be tested. - Consider options of how the EU system (reliance on ingredient safety) could be adapted for third countries such as China to facilitate trade.	i) Paper developed. ii) Outline of geographies and types of test where we think there is redundant animal testing to target focus. iii) Options for revising (possibly based on the EU model) including opportunities for reform identified (e.g. in China).	i) February 2014. ii) During 2014. iii) 2014 and ongoing.
2.5 Developing Action Plan priorities into an effective international communication and influencing strategy **(FCO, HO and BIS-SIN)**	Using BIS-SIN Global Partnership Fund, to support a UK collaboration with China for a two-day seminar, funded jointly by UK Government and the relevant pharmaceutical and cosmetics industries, for invited experts (government, academia and industry) from China and overseas (UK/EU/US) to be held in Beijing.	i) Organise seminar in Beijing to support development of standards for animal care, welfare and ethical use in research. ii) Work towards endorsement of standards by Chinese authorities. iii) Initiate a dialogue on harmonising pharmaceutical safety testing guidelines and develop a forward plan. iv) Explore a strategy to cease animal testing of cosmetics in China wherever it is not scientifically necessary.	i) March 2014. ii) Summer 2014. iii) March 2014 and ongoing. iv) March 2014 and ongoing.
	International lobbying, influencing and evidence gathering communications managed by FCO Science and Innovation Network, in partnership with BIS and Home Office leads, through the FCO global structure.	International Action Plan priorities delivered: Delivery Plan partners with an international component to their activity able to access FCO network efficiently/effectively with timely input of international feedback and evidence as required.	Ongoing.

Strategic Priority 3 – Promoting an understanding and awareness about the use of animals where no alternatives exist

Title/lead organisation(s)	Actions (underway or proposed)	Measures of success and key milestones	Timelines
3.1 Improving public understanding of animal research **(BIS)**	Improving public understanding of the context of animal research and the licensing framework. - Review the responses to animal research questions contained within the Public Attitudes Survey 2014 managed by Science and Society and forthcoming attitudinal survey. - Office of Life Sciences (OLS) leading Poll on animal research.	Previous polls (BIS) show an enhanced public understanding of the regulatory framework within which animals are used in the UK. i) 2014 poll launched ii) Evidence of enhanced public understanding through new poll results.	 i) March 2014. ii) Late 2014.
3.2 Increased transparency about actual severity **(HO)**	Disaggregation of data to report procedures according to their actual severity. More clearly separate the number of procedures associated with the breeding of non-harmful GM animals (involving no suffering) from painful procedures in animals.[Link to Action 1.6] Better inform the public about what animal research comprises (largely mild or sub-threshold) as well as to identify the most severe procedures and develop ways to reduce that severity.	i) Completion and review of pilot trial for retrospective (actual) severity reporting. ii) Development of Guidance on recording Actual Severity. iii) Commence project to map phenotyping of GA mouse strains to actual severity categories commenced (with external stakeholders e..g. MRC Harwell). iv) Completion of analysis of pilot data for limited publication. v) Publication of first complete year of retrospective actual severity data. vi) Provision of complete year data to the EU Commission.	i) December 2013. ii) January 2014. iii) March 2014. iv) July 2014. v) July 2015. vi) By November 2015.
3.3 Concordat on Openness and Transparency **(Academia, industry, health charities, funders, etc.)**	Concordat on Openness and Transparency to be more open about the ways in which animals are used in scientific, medical and veterinary research in the UK. - Concordat on Openness about animal research agreed between major funders, research organisations and industry. - IPSOS MORI report on Sciencewise supported public dialogue sessions will determine public expectations of openness, transparency and communication to inform the development of the Concordat on the use of animals in research.	i) Publication of declaration on openness. ii) Publication of Concordat. iii) Annual monitoring shows progress in implementation. iv) Polls show increased public understanding of the role of animal research.	i) Declaration on openness published October 2012. ii) Publication of Concordat Spring 2014. iii) Ongoing. iv) Next poll 2014.
3.4 Review of section 24 of ASPA **(HO)**	The Government to review section 24 of the Animals (Scientific Procedures) Act 1986 (ASPA). Section 24 provides for the protection of information, given in confidence, in connection with regulatory activities under ASPA. A breach of section 24 can result in criminal sanctions. The inflexible confidentiality requirements of section 24 are now out of step with government policy on openness and transparency and with the approach taken in other legislation, such as the Freedom of Information Act (FOIA). The intention is to design a more flexible framework that will protect proprietary rights, intellectual property and personal safety, provide greater transparency to assist public understanding, and not harm the competitiveness of the UK in the Life Sciences.	i) Public consultation on options for revision of section 24 commenced. ii) Response to public consultation reviewed and preferred option prepared. iii) Processes for legislative changes (as needed) pursued leading to revision of section 24.	i) By January 2014. ii) By May 2014. iii) Timing depends on legislative vehicle needed.

Glossary

3Rs	The principles of replacement, reduction and refinement – an ethical framework for conducting scientific experiments using animals humanely
AHVLA	Animal Health & Veterinary Laboratories Agency, an executive agency of Defra
ASPA	Animals (Scientific Procedures) Act 1986 (as amended in 2012)
ASRU	Animals in Science Regulation Unit, a unit of the Home Office responsible for regulating the use of animals in research under ASPA
AWERB	Animal Welfare and Ethical Review Body, a requirement of each research establishment licensed under ASPA
BBSRC	Biotechnology & Biological Sciences Research Council, an executive NDPB of BIS investing in bioscience research and training in the UK
BIS	Department for Business, Innovation and Skills
Cefas	Centre for Environment, Fisheries & Aquaculture Science, an executive agency of Defra
CFDA	The Food and Drug Administration responsible for registration, including pharmaceuticals, medical devices and cosmetics, in China
Defra	Department for Environment, Food and Rural Affairs
DH	Department of Health
ECHA	European Chemicals Agency responsible for the REACH Regulation
EOGRTS	Extended One-Generation Reproductive Toxicity Study
FCO	Foreign & Commonwealth Office
Fera	Food & Environment Research Agency, an executive agency of Defra
FRAME	Fund for the Replacement of Animals in Medical Experiments
FSA	Food Standards Agency, a non-ministerial department responsible for food safety and food hygiene across the UK
GA	Genetically altered (applied to animals)
GO-Science	The Government Office for Science which works within BIS and supports the Government Chief Scientific Adviser
HSE	Health & Safety Executive, an executive NDPB of the Department for Work & Pensions and the UK competent authority for REACH
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
in vitro	research using methods in components of an organism (e.g. tissue culture, cells, subcellular extracts or purified molecules)
in vivo	research using methods within a whole, living organism, usually an animal
MHRA	Medicines and Healthcare Products Regulatory Agency, an executive agency of DH responsible for registration of human medicines, vaccines and other healthcare products in the UK
MRC	Medical Research Council, an executive NDPB of BIS which aims to improve human health by supporting research in medical sciences
NC3Rs	The National Centre for the Replacement, Refinement & Reduction of Animals in Research
NDPB	Non-departmental public body
OECD	Organisation for Economic Co-operation and Development
PHE	Public Health England, an executive agency of DH which aims to protect and improve human health in the UK
REACH	Registration, Evaluation, Authorisation & restriction of Chemicals, an EU regulation which addresses the potential impact of chemicals on human health and the environment
RSPCA	Royal Society for the Prevention of Cruelty to Animals, a UK scientific animal welfare charity
TSB	Technology Strategy Board, an executive NDPB sponsored and funded by BIS
UFAW	Universities Federation for Animal Welfare – an internationally recognised, independent, scientific and educational animal welfare charity which first promoted the concept of the 3Rs
US FDA	US Food and Drug Administration, an operating division of the US Department of Health & Human Services responsible for ensuring that human and animal pharmaceuticals, medical devices and cosmetics in the USA are safe and effective
VICH	The International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
VMD	Veterinary Medicines Directorate, an executive agency of Defra responsible for registration of veterinary medicines, vaccines and other animal health products in the UK

URN BIS/14/589

ISBN 978-1-78246-264-4