Department for
Science, Innovation
& Technology

Replacing animals in science

A strategy to support the development, validation and uptake of alternative methods

CP 1429

Government of the United Kingdom
Department for Science, Innovation and Technology

Replacing animals in science

A strategy to support the development, validation and uptake of alternative methods

Presented to Parliament by the Parliamentary Under-Secretary of State for AI and Online Safety by Command of His Majesty

November 2025

CP 1429

This publication is available at www.gov.uk/official-documents

Any enquiries regarding this publication should be sent to us at enquiries@dsit.gov.uk

ISBN 978-1-5286-5871-3

E03395783 11/25

Printed on paper containing 40% recycled fibre content minimum

Printed in the UK by HH Associates Ltd. on behalf of the Controller of His Majesty's Stationery Office

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Ministerial foreword

The use of animals in science has been considered essential for providing insights into biology and disease, and for protecting humans and the wider environment, contributing to the creation of life-saving drugs and treatments.

More recently, there has been an increase in the use of alternative methods that can replace animals in some circumstances. However, the adoption of these alternatives has been limited by their ability to accurately replicate biological systems to satisfy the needs of regulators, science and quality control.

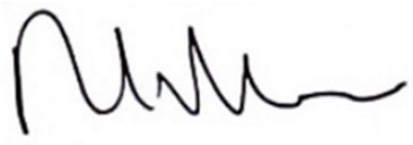
Now, new advances in technology – particularly AI and genomics, but also organoid and 3D cell systems – finally allow us to see a path to changing our reliance on animals in science.

Our manifesto committed us to partner with scientists, industry and civil society as we work towards the phasing out of animal testing. This strategy sets out how we will create a revolutionary research and innovation system that replaces animals with alternative methods wherever possible. It brings clear benefits for animal welfare and a host of economic and scientific impacts, through leveraging the UK's strong science base.

This strategy also marks a step-change in placing the UK at the forefront of international efforts to drive this crucial and exciting agenda.

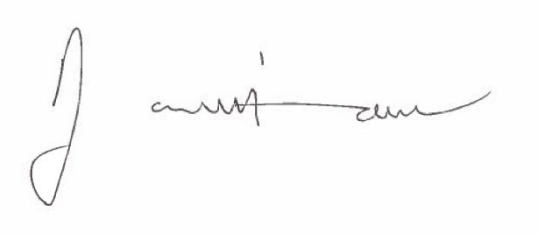
Phasing out the use of animals in science and product development must be supported by reliable and effective alternative methods, so this strategy aims to create a system that drives their use. However, as this strategy is implemented, we recognise that some animal research will continue, due to the maturity of alternatives available. In the meantime, we will continue to support and enable well justified and designed animal research where alternatives do not exist.

In creating this strategy, we are proud to take the next steps on our journey to phasing out the use of animals in all but exceptional circumstances, continuing the UK's proud tradition of animal welfare, while also reaping the clear and exciting benefits that new alternatives offer.[1]



Lord Vallance of Balham
Minister of State for Science, Innovation, Research and Nuclear
Department for Science, Innovation and Technology

[1] This policy is reserved in all four nations of the United Kingdom.



Rt Hon Lord Hanson of Flint
Minister of State
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Baroness Hayman of Ullock
Parliamentary Under-Secretary of State for Biosecurity, Borders and Animals
Department for Environment, Food and Rural Affairs

Executive summary

This Government is proud to lead a new era in advancing innovative and effective approaches to scientific research and development. We are committed to delivering on our manifesto pledge to “partner with scientists, industry, and civil society as we work towards the phasing out of animal testing”. This reflects not only our deep commitment to animal welfare but also our belief in the economic, scientific, and societal benefits that come from investing in and phasing in modern alternatives. This Government recognises the urgency of this transition and is determined to drive meaningful change through coordinated, cross-governmental action.

Our vision is for **a world where the use of animals in research and development is eliminated in all but exceptional circumstances** achieved by creating **a research and innovation system that replaces animals with alternative methods wherever possible**. This will include a wide range of new and validated alternatives used in discovery and translational research, and new methodologies for chemical and environmental testing, and safety and toxicity testing of potential novel human and veterinary medicines. This strategy lays out the steps we, the Government, will take over the next five years towards achieving this vision across the whole of the UK. We also highlight specific instances of animal use where we will take immediate and near future action to ensure alternative methods are applied going forward.

The use of animals in science provides an insight into human and animal biology and disease. Animals are also used in many sectors to test the safety and efficacy of chemicals in consumer products, and in new human and veterinary vaccines, medicines and medical devices before they are trialled in their intended populations or marketed. Enabling the 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, and we will continue to support the appropriate use of animals where reliable and effective alternatives are not yet available. But we will not accept a slow pace of change when scientific and technical advances mean that a faster transition away from animal use is possible.

Recent scientific advances have provided new impetus to the development of alternative methods that replace, reduce and refine the use of animals in research (the 3Rs). There is also a rapidly accelerating global movement to adopt alternative methods in the life sciences. The maturity of these methods differs across scientific and regulatory sectors, but alternative methods are being applied in a wide range of contexts across discovery research, veterinary science, drug and chemical discovery, toxicity testing, and clinical investigations. We are at a tipping point where international regulatory and political commitment, technological capabilities and scientific advances are converging to create a system capable of delivering the scientific, commercial, societal, economic and animal welfare benefits offered by alternative methods.

The term ‘alternative methods’ describes a broad range of tools and technologies that can reduce or replace animal use across the whole of the bioscience landscape. They are being applied in a wide range of contexts and have benefits including specificity, sensitivity, species relevance and speed, but also disadvantages, such as a current inability to model the whole organism for hazard definition or replicate complex endpoints in a single assay. Only a few of these methods have, to date, been fully validated or qualified to replace animals for specific purposes, and therefore adoption for discovery

research and uptake into policy and regulatory use has been patchy and limited. This strategy covers the whole range of uses of animals in science and has been developed to accelerate the development, validation and adoption of scientifically evidenced alternative methods in discovery, applied, translational and regulatory research and testing.

The strategy will build on the UK's well-established life sciences research system enabling it to respond with greater agility to opportunities in the rapidly evolving alternative methods landscape. It has six objectives:

I. Accelerate the replacement of animals in science to phase out their use.

II. Achieve equal or better research and testing outcomes using alternative methods.

III. Drive private investment in alternative methods to boost innovation and growth.

IV. Improve regulatory confidence and acceptance of alternative methods.

V. Create infrastructure and partnerships to unlock value from UK data.

VI. Position the UK as a global leader in alternative methods.

We, the Government, will deliver this by focusing on five key commitments:

I. **Driving alternative method development and uptake in discovery research:** We will incentivise the development and adoption of alternative methods. This will be delivered through (i) increased and sustained investment focused on animal replacement; (ii) better animal research approval and dissemination mechanisms to assess whether animal use is required or whether alternatives could be used; and (iii) a workforce with the necessary skills set to implement the uptake of new alternative methods quickly and effectively. We will establish a new preclinical translational research hub to bring together data, cell engineering, genomic technology, and expertise to create a pipeline of novel translational medicine models.

II. **Accelerating alternative methods validation and uptake for regulatory decision making:** We will establish a national approach to accelerating the validation and regulatory acceptance of alternative methods. At its core will be a new UK Centre for the Validation of Alternative Methods (UKCVAM) that will coordinate a cross-sector network of public and private laboratories and facilitate engagement between policy makers, regulators, industry end users and alternative method developers.

III. **Delivering the transformative potential of our data assets:** We will create national infrastructure, collaborations and regulatory frameworks to expedite equitable and secure access to high-quality datasets to enable data-driven innovation that reduces animal use and enables the use of alternative methods. This will include increasing investment in data-driven biology, establishing data sharing platforms to facilitate access to public and private data repositories, setting clear standards for data quality and interoperability, widespread adoption of AI methods to assess potential safety and toxicity profiles, and developing regulatory guidance to support data-driven and AI-informed decision-making. We will be working with industry and regulators to make their historic data sets available for use, as part of UKCVAM.

IV. **International leadership and cooperation:** We will establish the UK as a global leader in the regulation and science of alternative methods, ensuring our participation on key forums and international committees in this space. We will also expand existing and establish new partnerships with international regulators to identify internationally agreed priorities of mutual importance, explore data sharing possibilities and AI projects to assess toxicity, safety and efficacy from existing data sets, and accelerate the global acceptance of validated alternative methods.

V. **Effective governance culture:** We will establish governance structures with diverse stakeholder representation to oversee progress and delivery of the actions described in this strategy. This will include a set of key performance indicators with which to assess delivery of the strategy and forming a cross-governmental Ministerial group on alternative methods, chaired by the Science Minister. We will have a publicly available dashboard of progress against key deliverables.

This strategy has been developed involving stakeholders from industry and regulatory agencies representing chemicals, agriculture, food, and pharmaceutical sectors, and many of the actions and commitments we pledge are applicable across multiple sectors.

Part I – The current UK context of animals and alternatives research

Introduction

Despite the known limitations, the use of animals in science provides an important insight into the complexity of human and animal biology and disease. They are also used to test the safety and efficacy of chemicals in consumer products, and in ensuring the safety of new human and veterinary vaccines, medicines and medical devices before they are trialled in their intended populations or marketed. Enabling the properly regulated use of animals is currently essential to improving the health and lives of humans and animals and to the safety and sustainability of our environment. It also plays a crucial role in advancing UK research across fields including the environmental, agricultural, veterinary, animal welfare, medical, and life sciences sectors, forming the foundation for essential discoveries that improve outcomes for both humans and animals.

In the UK, the Animals (Scientific Procedures) Act 1986 (ASPA) provides the legislative framework governing the use of animals in research. It mandates the development and application of alternative methods, including non-animal methods, as part of implementation of the 3Rs (the Replacement, Reduction and Refinement of animals used in research – see Box 1). Furthermore, under ASPA, research which uses animals is only conducted where there is no alternative available, using the fewest number of animals and procedures which keep suffering to a minimum.

Box 1 – The 3Rs[2]

Replacement of the use of animals with scientifically robust alternatives in areas where they otherwise would have been used.

Reduction in the number of animals used to the minimum consistent with the scientific aims.

Refinement of testing methods and housing and husbandry to minimise the pain, suffering, distress, or lasting harm that research animals might experience across their lifetime.

'Alternative methods' (sometimes called alternative strategies) is a catch-all term, meaning "scientific methods and testing strategies which do not use protected animals, or which (compared to existing scientific methods and testing strategies) use fewer protected animals".[3] There is a rapidly accelerating global movement to adopt alternative methods in the life sciences that reflects advancements in non-animal technologies. Alternative methods are being applied in a wide range of contexts and have benefits including

[2] See Glossary for full definition

[3] ASPA regulates the use of protected animals in scientific procedures that may cause harm. Protected animals include all living vertebrates (except humans) and cephalopods. Mammal, bird, and reptile embryos are protected in the last third of gestation/incubation period, while fish and amphibian larvae gain protection once they can feed independently. Cephalopods are protected from hatching.

specificity, sensitivity, species relevance and speed,[4] but also disadvantages, such as a current inability to model the whole organism for hazard definition or replicate complex endpoints in a single assay. While many innovative methods have been developed in recent years, a relatively small subset has been qualified or validated for use, limiting their wider uptake in discovery research and regulatory testing. Where they are used, it is often alongside animal studies to ensure that these studies generate the most meaningful data, or in discovery research and non-regulatory settings for early decision making. However, as they evolve, so too will their capacity to replace animal use. We recognise that asking alternative methods to replicate what is currently seen in animal studies is often not the right question. The right question is whether the alternative methods give information necessary to make the appropriate decision in relation to biology, efficacy, safety or toxicity.

The UK has invested considerably in the development and use of alternative methods for the last 20 years, primarily through the National Centre for the 3Rs (the NC3Rs), and we are now at a tipping point in the transition to alternative methods. The advent of AI and its application to large data sets, the development of organoid and new cellular models, and advances in genomics, proteomics and other measurement in humans offer real opportunities of rapid change. Global regulatory roadmaps, major funding initiatives, and mounting societal pressure are converging with these technological advances, advancement in scientific techniques and political commitment to create a system capable of delivering the scientific, commercial, societal and animal welfare benefits offered by non-animal approaches.

Why are animals used in science?

For decades, animal models have been fundamental to life sciences research. Their use is only licensed for specific permissible research and testing purposes[5] that offer insights into health and disease in both humans and animals, or in developing and evaluating new therapies, ensuring biocompatibility of medical devices, and the safety of people, animals, and the environment, making them essential tools in translational research (see Box 2). The Government will continue to support carefully regulated and ethically conducted animal research, including in those species offered special protection under ASPA (e.g. cats, dogs, horses and non-human primates) when no viable alternative methods are available, to safeguard humans and the environment during the development of medicines, medical devices, and chemicals. However, we will not accept delays in progress when scientific and technological advances make a more rapid shift away from animal use feasible.

Understanding human and animal biology

A significant portion of how human and animal biology operates is conserved across species, not only in essential functions such as breathing, digestion, sensory perception, and reproduction, but also at the cellular level. Where biology is shared with humans, it allows researchers to investigate physiological mechanisms through animal studies, which are often not feasible in human subjects, including to provide critical insights into what occurs when these mechanisms fail. Animal use to address discovery research questions which aim to understand the fundamental concepts and principles of human and animal

4 For example, see https://www.nature.com/articles/s43856-022-00209-1

5 https://www.gov.uk/government/publications/the-operation-of-the-animals-scientific-procedures-act-1986

biology accounted for just over half (52%) of all regulated experimental procedures using animals in Great Britain in 2024.[6]

Modelling disease

Advancing our ability to combat diseases in both humans and animals relies on a deep understanding of complex and often subtle biological processes. Significant physiological and genetic similarities can make animals useful in studying complex human biological processes, disease pathogenesis and therapeutic interventions. Genetically, species like mice share approximately 85% of their genome with humans, making them widely used for studying conditions such as cancer, metabolic disorders and neurodegenerative diseases. Advances in genetic engineering have further enhanced the relevance of animal models, enabling the development of genetically altered animals (organisms with genes removed or inactivated from, or human genes inserted into, their DNA) to study human-specific diseases, including Alzheimer's disease, cystic fibrosis and some cancers. But there are clear limitations to the information that animal studies provide.

Understanding the differences between humans and animals can also be informative. The resistance of certain species to human diseases may offer clues about disease protective mechanisms. Identifying variations in gene expression between humans and other animals, for example, could reveal why certain diseases occur, or how we prevent progression.

Developing and testing new medicines and medical devices

Animal models are used in research for developing medicines, chemicals (including industrial chemicals and agrochemicals), and medical devices, offering insights into how substances move through and act in the body (i.e. pharmacokinetic and pharmacodynamic processes), toxicity, biocompatibility and efficacy. They help evaluate complex physiological interactions. Medicines, including vaccines and other biologics such as growth factors and monoclonal antibodies, undergo rigorous animal testing to assess safety and efficacy. For example, Herceptin, a monoclonal antibody therapy for HER2-positive breast cancer, was developed through extensive animal research. The discovery of the HER2 protein in rat tumours, followed by the production of HER2-targeting antibodies in mice and hamsters, were crucial steps in its development. There are many such examples where studies in animals have resulted in major advances in improving human and of course animal health.

Medical devices also rely heavily on animal studies for their development and validation. Devices like pacemakers, prosthetic joints and diagnostic imaging systems must demonstrate biocompatibility, functionality and safety *in vivo*. For example, the development of mechanical heart valves involved extensive testing in sheep and pigs due to their anatomical and physiological similarities to human cardiac systems. Surgical techniques, including organ transplantation, have similarly been refined through animal research, enabling significant advances in clinical practice.

Protecting the safety of people, animals and the environment

Veterinary medicines and chemicals that can enter the environment (e.g. those intended for agriculture and industrial processes) are tested to evaluate their potential risks to human health, ecological impact and environmental sustainability. Crop protection

[6] https://www.gov.uk/government/statistics/scientific-procedures-on-living-animals-great-britain-2024

technologies will remain as one of the key priorities needed by farmers and growers in the UK and worldwide. Research into new products, such as biological crop protection systems, will be needed to understand chemical bioaccumulation and environmental exposure, as these substances can persist in ecosystems, affecting water, soil and air quality. Animal models help to simulate long-term exposure scenarios, enabling researchers to predict the ecological consequences of chemical use.

In vitro methods provide critical early-stage insights into the intended beneficial effects of new medicines and chemicals and their potential risks. They can also be tailored to investigate the sensitive life stages where organisms are particularly susceptible to perturbation. However, many regulators across sectors, such as the UK Medicines and Healthcare products Regulatory Agency (MHRA), Veterinary Medicines Directorate (VMD), Health and Safety Executive (HSE), and Food Standards Agency (FSA), together with international counterparts including the European Medicines Agency (EMA), U.S. Food and Drug Administration (FDA), European Chemicals Agency, the U.S. Environmental Protection Agency (EPA) and the World Health Organisation (WHO) still require data from animal studies, especially to understand complex and/or long term effects on whole body systems. In instances where humans are the only pharmacologically-relevant species however, for example for some monoclonal antibody and protein-based therapies, some regulators (e.g. FDA, MHRA, EMA, and the Australian Therapeutic Goods Administration (TGA)) are already accepting routes to approval that do not require the usual animal studies.

UK regulators and governmental agencies (including the Centre for Environment, Fisheries and Aquaculture Science (Cefas), Environment Agency (EA), FSA, HSE, MHRA, VMD and UKHSA) are involved in activities to expedite the adoption of alternative approaches through interactions with the bodies responsible for internationally agreed standards in testing such as ICH,[7] ISO,[8] VICH,[9] European Pharmacopoeia,[10] and OECD.[11] Furthermore, UKHSA, the Department for Environment, Food and Rural Affairs (Defra), and the NC3Rs are actively engaged in supporting the development, validation and uptake of new approach methodologies as internationally agreed standardised test guidelines.[12] Recent consortia and industry body recommendations and changes in global policy around the use of alternative methods for generating data to support regulatory submissions are a major shift in the right direction, and all countries that are members of OECD or ICH including the UK,[13,14] are fully committed to embedding the 3Rs in chemical safety testing. There is a need to build on and consolidate these activities to put the UK at the forefront of development and validation with dedicated facilities and expertise.

7 International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH); www.ich.org.

8 International Organization for Standardization; https://www.iso.org/home.html

9 Veterinary International Conference on Harmonization (VICH); https://vichsec.org/

10 European Pharmacopoeia; https://www.edqm.eu/en/european-pharmacopoeia

11 Organisation for Economic Co-operation and Development (OECD); www.oecd.org

12 https://nc3rs.org.uk/news/incorporating-nams-medicines-development-insights-regulators-industry-and-academia

13 https://nc3rs.org.uk/uk-chemicals-regulation-vision-january-2024

14 Recommendations for the Adoption of New Approach Methodologies (NAMs) in UK Chemical Regulation

Box 2 – Animal research benefiting humans, animals and the environment

Chemicals that can mimic or block hormones (called endocrine disruptors) can be found in products released into aquatic environments where they could significantly impact the reproductive development and function of humans and other wildlife. The OECD has adopted a toolbox of tests that are used to assess such developmental and reproductive effects. This includes studies examining effects in fish species such as zebrafish, fathead minnow and Japanese medaka, aimed at protecting fish populations from endocrine disrupting chemicals.[15]

Animal research in rats and mice played a critical role in developing anti-TNF therapy for rheumatoid arthritis (RA). Rodent models demonstrated that TNF-α was a key cytokine driving joint inflammation. Neutralising TNF-α was shown to reduce inflammation in RA patients, leading to the development of anti-TNF drugs like infliximab, confirming TNF-α's pivotal role and translating preclinical findings into very effective treatments for a range of human diseases.[16]

Researchers at the Royal Veterinary College, London, have successfully demonstrated the utility of Functional Electronic Stimulation (FES) as an alternative treatment to surgery for recurrent laryngeal neuropathy (RLN) in horses. RLN is a common condition that causes a narrowing of the airway making it difficult for horses to breath normally. The condition is caused by a decline in function of the cervical vagus nerve that controls the muscles that open the larynx, leading to weakness of the muscle over time. Surgery is the current standard treatment but is only successful 50% of the time and comes with significant risks. FES represents a supportive treatment to promote laryngeal functional recovery after RLN injury.[17]

How many animals are used?

The UK utilises a significant number of animals to deliver our diverse experimental needs across fundamental and translational research, veterinary and human medicines and medical devices development, and regulatory drug, chemical, and environmental safety testing. In 2024, 2.64 million scientific procedures[18] involving animals protected under ASPA were carried out, the lowest since 2001, continuing the trend of decreasing animal use over the past decade (Figure 1), supported in part through our continued investment in the NC3Rs.

Most procedures (95%) used rodents (mice or rats), fish and birds. Just over half of all procedures (54%) were for experimental purposes such as basic research and the

[15] https://www.oecd.org/en/publications/2011/07/test-no-234-fish-sexual-development-test_g1g14f44.html

[16] Maini, R *et al* (1998) Arthritis Rheum 41(9); 1552-1563 DOI: 10.1002/1529-0131(199809)41:9<1552::AID-ART5>3.0.CO;2-W

[17] Cerone, M *et al* (2019) Muscle & Nerve 59(6) 717-725 DOI: 10.1002/mus.26460

[18] The number of procedures exceeds the number of animals used, as some animals are reused and counted as separate, additional procedures. Procedures also include breeding to produce genetically altered animals for research. These animals produce genetically altered offspring for experiments but are not used themselves.

development of treatments, safety testing of pharmaceuticals and other substances. Just over 2,646 experimental procedures involved dogs (0.2%), and 1,936 involved non-human primates (0.14%). In these cases, the majority were used for testing the safety of products and devices for human medicine and veterinary medicine required by regulators. The main fields of basic research using animals were the nervous system (170,880 procedures, 12% of all experimental procedures), the immune system (137,113 procedures, 10% of all experimental procedures) and cancer research (101,418 procedures, 7% of all experimental procedures). Regulatory toxicity testing accounted for just over 11% of all experimental procedures (156,900), mainly using rodents and fish. No animals were used in the testing of cosmetics or household products.

Just under half of all procedures in 2024 (46%) were for the creation and breeding of genetically altered animals, with 99% of these being mice or fish, primarily used in discovery and medical research to understand gene function and create models of human disease to elucidate disease pathways and allow the assessment of new therapies. As our understanding of the human genome expands, we are learning more about the effects of genetic variation on both health and disease, and some of these animal models are likely to continue to provide insights into the complex mechanisms underlying health and the potential of specific targeting of new treatments for diseases.

The UK's regulation of animals in science aims to deliver high standards of animal protection, compliance and welfare, and to ensure that animals are only used when there is no alternative. However, the Rawle Report[19] published in 2023, identified gaps in the implementation of our regulatory system, particularly for consideration of replacement approaches for both academic-led discovery and translational research. This was attributable largely to a lack of specific knowledge at various stages along the ethical review approval process about available alternative methods, their robustness and where it is scientifically appropriate for them to be used.

The use of alternative methods

The use of alternative methods across the life sciences is gaining significant momentum globally, with over 10,000 peer reviewed scientific publications attributable to the variety of applications and roadmaps towards acceptance and integration of alternative methods over the past two and a half years.[20] Moreover the advances in techniques to understand human biology mean that many scientists are moving to using these new approaches rather than continuing to use animals. The UK has a strong track record in supporting the development and adoption of alternative methods for both discovery and translational research. We have a renowned research base comprising world-leading universities, a vibrant life sciences sector (supported by the Government's modern Industrial Strategy and Life Sciences Sector Plan), government agencies (e.g. FSA, Cefas, UKRI, MHRA, VMD, and UKHSA amongst others) developing and promoting the 3Rs in their work and a strong commercial and entrepreneurial system to support spin-outs, start-up companies and contract research organisations (CROs).

Our national 3Rs centre (NC3Rs) was the first organisation of its kind globally and plays a pivotal role in encouraging scientific engagement in the 3Rs and alternative methods. It

[19] https://nc3rs.org.uk/news/new-report-3rs-animal-research

[20] See roadmaps from the Dutch National Institute for Public Health and the Environment, European Commission, U.S. Environmental Protection Agency, U.S. National Toxicology Programme, and Health Canada, as examples.

was established in response to a House of Lords committee recommendation to increase investment and activity in the 3Rs in the UK.[21] Their science-focused and evidence-based approach has led a comprehensive transformation in the level of activity and support for developing 3Rs approaches across the life sciences and regulatory sector in the UK and internationally. Over the last five years they have worked in partnership with 300 organisations, nearly 70% of which are international or multinational; and since 2004 funded nearly 550 research projects and early career awards (PhD studentships and early career fellowships), nearly three-quarters of which have focused on replacement research and method development.

The market potential for alternative methods is substantial. It has been estimated that by 2030 the global non-animal technologies for life sciences market will be worth $29.4 billion,[22] and the UK is well positioned to capitalise on this. However, challenges for development, validation and the more widespread adoption of alternative methods remain, as new alternatives are conceived and evolve.

Current and emerging alternative methods

Over the last 50 years, we have witnessed an explosion in the scientific and technical advancements of underpinning tools and technologies that have the potential to replace animals in science. Advancing our understanding of human biology and pathophysiology requires studying humans and the use of human relevant models. This includes cell culture models, bioengineering approaches, the availability of human tissue and stem cell technologies, and the evolution of mathematical and *in silico* modelling with the full promise of AI yet to be seen. For example, the existence of large repositories of data on toxicology and chemical structures provides a major opportunity, particularly with the advent of AI to assess trends and patterns that otherwise may have been difficult to determine. Alone, or in combination, these approaches offer exciting animal replacement opportunities when applied to complex biological questions.

Early scientific research relied heavily on 2D cell cultures, where cells are grown in flat monolayers on plastic surfaces. While these models provide valuable basic insights into cellular biology, drug mechanisms and potential toxicity, their simplicity often limits their ability to mimic the intricate dynamic environment of living tissues. The advent of 3D cell culture systems and organoid models marked a pivotal shift. These models enabled cells to grow in three dimensions with a host of physiologically relevant, structurally or functionally supportive cells and extracellular matrices in a tissue microenvironment more representative of human tissue. More complex models such as spheroids, organoids, tissue-engineered and bioprinted constructs have become key tools in fields such as oncology, neurobiology, and regenerative medicine (see Box 4).

The rise of stem cell technologies, particularly induced pluripotent stem cells (iPSCs), provide a renewable and patient-specific source of human cells for studying disease mechanisms, drug and chemical screening, and regenerative therapies. Gene editing technologies (such as CRISPR) are also being applied to introduce disease-associated

[21] https://publications.parliament.uk/pa/ld200102/ldselect/ldanimal/150/15001.htm

[22] From Pharmiweb.com, accessed 4 November 2024. https://www.pharmiweb.com/press-release/2024-05-08/non-animal-alternative-testing-market-size-to-achieve-usd-294-billion-by-2030-fueled-by-a-cagr-of#:~:text=Allied%20Market%20Research%20has%20published,%F0%9D%9F%93%25%20from%202022%20to%202030.

mutations to complex cell models to create more physiologically relevant human disease models.[23]

Over the last decade, microphysiological systems, including organ-on-a-chip technologies – three-dimensional models of human tissues and organs that simulate their physiological functions and microenvironment – have emerged as sophisticated *in vitro* models offering the potential for greater human relevance. For example, liver-on-a-chip models have been used to study drug metabolism and hepatotoxicity, while lung-on-a-chip systems have enabled investigations into respiratory diseases and nanoparticle toxicity.

Furthermore, the ability to connect multiple organ-on-a-chip devices potentially offers a platform to study inter-organ interactions and systemic effects and allow the *in vitro* investigation of pharmacokinetics, pharmacodynamic, metabolic, toxicological and genomic effects of drugs and chemicals in the body. Regulatory agencies are recognising the potential of alternative methods, paving the way for their broader adoption.

Advances in computational power over the last few decades have also transformed computational modelling from simple mathematical equations to highly sophisticated simulations powered by AI. Early computational approaches relied on relatively simple deterministic models to describe biological processes, such as enzyme kinetics or population dynamics. While these models provided valuable theoretical frameworks, they may have lacked the ability to capture the complexity and variability of biological systems. That is changing with AI.

The integration of systems biology approaches allowed researchers to construct large-scale models of cellular pathways, metabolic networks, and gene regulatory circuits, enabling hypothesis generation and testing *in silico*, reducing the need for exploratory animal studies. For example, a CRACK IT-funded research project[24] has developed an integrative *in silico* platform, called Xpaths that provides information on the relationship between specific genes and specific physiology, or specific compounds and specific effects, across several model organisms. Using Xpaths, it is possible to test compound-induced effects on developmental and reproductive toxicity in multiple test methods. Combining this information enables predictions of the effect of the same compound in humans and other mammals, potentially reducing the number of animals used to meet regulatory testing requirements.

Recent advances in AI have enabled researchers to identify patterns in large, complex datasets, making them invaluable for tasks such as drug discovery, disease classification and biomarker identification. The utility of this type of technology was demonstrated in the AlphaFold[25] project that predicted protein structures with atomic accuracy from just their amino acid sequences, massively advancing our ability to understand protein structures. Machine learning models trained on high-throughput screening data can predict drug toxicity and efficacy prior to animal testing, significantly reducing the number of chemicals tested in animals. Companies like Isomorphic, Labgenius Therapeutics, HealX, and Exscientia (now Recursion) are attempting to use data sets and AI to undertake drug discovery without the need for animal experimentation.

Through Genomics England, UK Biobank and the NHS, researchers have unparalleled access to extensive datasets of medical, genetic and health information from patients and

[23] https://nc3rs.org.uk/news/ps90k-awarded-develop-functional-genomics-screens-3rs-technologies

[24] https://nc3rs.org.uk/crackit/dartpaths

[25] https://alphafold.ebi.ac.uk/

healthy volunteers. This is an invaluable resource for developing, training and refining AI models that can be used to mine these datasets to uncover novel associations, predict disease progression, and inform personalised medicine strategies without using animals. The ability to select targets for new drugs by using these genomic and phenotypic datasets is revolutionising drug discovery.

One of the most exciting frontiers in life sciences research lies in the integration of complex human-relevant *in vitro* models with computational technologies to understand disease progression and identify therapeutic targets in the intended population, and how chemicals interact with the body and environment. These combinatorial approaches allow researchers to address increasingly complex biological questions with greater precision and efficiency. This is especially valuable in drug discovery and development, where combining AI-driven modelling and organ-on-a-chip platforms could improve prediction of human drug responses, reducing reliance on animal testing and addressing interspecies differences. Equally in the hazard characterisation of chemicals, utilising new AI based defined approaches can predict the likelihood and potency of a chemical to cause skin sensitisation, or in defining key events in adverse outcome pathways, removing the need for testing on animals.[26]

The continued development of these alternative method technology platforms promises to further reduce our reliance on animal models, especially if they can answer biological questions across the complexity of evolving advanced chemical and pharmaceutical targets. Advances in bioengineering, such as bioprinting and nanotechnology, are expected to enhance the complexity and functionality of *in vitro* models. Integration with next generation sequencing,[27] and the data from different “omes” (genome, transcriptome, proteome, epigenome, etc) will improve the relevance and translatability to humans of alternative methods and provide valuable insights into responses at the cellular and sub-cellular level. The increasing sophistication of AI will ultimately enable the creation of some model of virtual humans, capable of simulating individual variability and predicting personalised treatment outcomes. Investing in developing human-based models will also help us prepare for the development and implementation of new vaccines, more rapidly than traditional pathways of generating transgenic animal models that may not translate fully to humans. Alternative methods will need to adapt and evolve to make them suitable to biological technologies across sectors as new types of tools, modalities and targets arise.

Applying alternative methods across the life sciences

Alternatives to the use of animals have been adopted to different degrees across fundamental and translational research, veterinary and human medicines development, and regulatory drug, chemical, and environmental safety testing (see Box 4). In 1998, the UK banned the use of animals in the testing of cosmetics. This was facilitated by the availability of some advanced and scientifically valid non-animal alternatives to test the safety of specific ingredients and the fact that cosmetic ingredients were already well-studied for safety. A complete ban was effective throughout the EU from 2013, unless necessary for occupational worker testing for instance.

[26] https://ntp.niehs.nih.gov/whatwestudy/niceatm/test-method-evaluations/skin-sens/da

[27] Next generation sequencing enables the interrogation of hundreds to thousands of genes at one time in multiple samples in a single analytic run. It enables the investigation of multiple genomic features, including nucleotide variation and mutation, and is applied in many applications including cancer tumour analysis.

Discovery research and disease modelling

The complexity of human and animal biology requires a variety of experimental approaches to investigate fundamental biological processes. Alternative methods are a crucial part of a researcher's toolkit to enable the more precise investigation of cellular mechanisms, gene function and molecular interactions. For example, relatively simple 2D models of liver derived HepG2 cells have been used to study basic cholesterol deposition relevant to atherosclerosis and heart disease. More complex 3D spheroids derived from patients or healthy human volunteer biopsies or iPSCs are being applied to study cell proliferation or apoptosis in cancer aetiology and human-specific processes like neural development and synaptic connectivity. Irrespective of their scale or level of complexity, these cell-based alternative methods provide mechanistic insights as part of physiological and metabolic pathways which can be challenging to dissect in animal models.[28, 29]

Translational science and safety testing

Traditional drug and chemical discovery pipelines are resource-intensive, with high failure rates. Alternative methods can help bridge this gap by providing additional tools for identifying drug targets and for screening candidate molecules and assessing their safety (and efficacy) earlier in the development process. High throughput screening (HTS) using simple cell-based assays can screen thousands of compounds rapidly. Coupled with automated imaging and data analysis, HTS platforms identify potential candidates and assess toxicity profiles with unprecedented speed, enabling companies to identify earlier those compounds likely to fail, before they are tested in animal toxicity tests. If combined with AI tools based on existing libraries of compound structures and known toxicity profiles, there is an opportunity to be far more predictive early in the process and well before any animal is used. Modern human genomics can identify causal pathways of disease or potential harms in a way not previously possible. This changes the ability to pick a drug target early with much greater confidence and without the need for certain types of animal studies.

Regulatory frameworks, including those established by the VICH, ICH and OECD are increasingly considering how alternative methods can be integrated in their recommendations. Toxicology testing has particularly benefited from alternative methods. *In vitro* assays, such as those measuring cytotoxicity, genotoxicity, endocrine activity, and organ-specific toxicity, provide critical data on the safety of chemicals and pharmaceuticals. For example, for pharmaceuticals, since 2005 the ICH has required that *in vitro* ion channel assays be conducted to evaluate the risk of cardiac arrhythmia of new drugs.

The regulations and maturity of alternative methods across chemicals and pharmaceuticals have accelerated and evolved at different rates. There are several accepted alternative methods in use for the safety assessment of chemicals in the environment, consumer products, and cosmetics. These focus mainly on simple endpoints such as the use of reconstructed human epidermis models widely used for assessing skin and eye irritation. The OECD test guideline on the use of an *in vitro* skin corrosion assay was first released in 2005,[30] and since then several test guidelines ranging from skin

[28] https://www.nature.com/articles/s41586-025-08808-3

[29] https://www.nature.com/articles/s41420-021-00812-6

[30] https://www.oecd.org/en/publications/test-no-431-in-vitro-skin-corrosion-human-skin-model-test_9789264071148-en.html

irritation,[31] skin sensitisation,[32,33] and short-term exposure[34] have been developed and adopted as international test guidelines.

Alternatives to the use of protected species have been developed for fish acute toxicity and bioaccumulation endpoints, and research is ongoing to identify suitable replacements for long-term toxicity tests (Box 3). The Environment Agency (EA) is actively involved in this work and will continue to seek opportunities to support further research and the use of environmental alternative methods within UK REACH, enhance understanding of the applicability domains of relevant methods, raise awareness among stakeholders, and contribute to the development of case studies that support the international acceptance of new methods.

Gaps in how well alternative methods can reliably and consistently replicate the complexity of multi-cellular mammalian tissues, organs, or whole organisms remain. This is particularly evident in areas such as assessing the long-term effects of drugs and chemicals for their potential to cause cancer, understanding how substances impact foetal development and reproduction, and studying neurotoxicity. Since *in vivo* chronic assessments can last for up to two years, current alternative methods are unable to fully mimic these exposure conditions. However, by breaking down the biochemical and mechanistic processes behind observed adverse effects, individual alternative tests can contribute to a combinatorial, integrated approach. Coupling this with historic data sets and the use of AI and the increasing numbers of predictive biomarkers in humans should enable far better prediction of potential harmful effects.

Box 3 – Replacing mammalian acute toxicity tests

To determine potential human health effects of manufactured chemicals, acute animal toxicity studies are mandatory under some current regulatory requirements and legislation. These studies, typically conducted in rats, aim to determine the dose or concentration of a substance that causes death in 50% of the test animals (LD50/LC50). They are among the few tests where lethality is the intended endpoint and are associated with the highest levels of animal suffering. While no longer required for pharmaceuticals, they remain mandatory under current regulatory frameworks for chemicals and agrochemicals, with several OECD guidelines still in use globally.

[31] https://www.oecd.org/en/publications/2021/06/test-no-439-in-vitro-skin-irritation-reconstructed-human-epidermis-test-method_g1g59b2f.html

[32] https://www.oecd.org/en/publications/2023/07/test-no-442e-in-vitro-skin-sensitisation_g1g6ece4.html

[33] https://www.oecd.org/en/publications/2023/07/guideline-no-497-defined-approaches-on-skin-sensitisation_30b1718f.html

[34] https://www.oecd.org/en/publications/test-no-491-short-time-exposure-in-vitro-test-method-for-identifying-i-chemicals-inducing-serious-eye-damage-and-ii-chemicals-not-requiring-classification-for-eye-irritation-or-serious-eye-damage_9789264242432-en.html

Validated non-animal methods exist for predicting acute effects such as skin and eye irritation and sensitisation, but replacing oral and inhalation acute toxicity tests remains more complex. While there is significant international activity to develop non-animal approaches for acute toxicity testing – including *in silico* models such as CATMoS (Collaborative Acute Toxicity Modeling Suite) for oral toxicity and *in vitro* systems like EpiAirway™ for inhalation – these methods are still undergoing evaluation and have not yet been accepted as stand-alone replacements in regulatory frameworks. Part III of this strategy sets out cumulative commitments to drive and accelerate the necessary scientific, cultural, and regulatory changes needed to replace acute toxicity animal testing with validated alternatives, using a structured approach to prioritise funding and support. Over time we would expect this work to significantly reduce the amount of toxicity testing undertaken. Until full replacement is possible, the UK is supporting refinement approaches, led by the NC3Rs, to reduce animal suffering. This includes promoting the use of "evident toxicity" – clinical signs that predict lethality – as an endpoint instead of death and influencing international guideline revisions.

The NC3Rs, UKHSA and many CROs have played a key role in the adoption of OECD TG 433 for inhalation studies, which uses evident toxicity, and continues to work with regulators and industry to phase out guidelines that rely on lethality, such as OECD TG 403. For oral studies, OECD TG 420 allows the use of evident toxicity, but uptake remains limited due to lack of guidance and regulatory uncertainty. Ongoing work aims to validate evident toxicity for classification and labelling purposes and encourage harmonised global adoption.

Product development – clinical application

AI-driven technologies can help bridge the gap between traditional animal studies and human exposure. These tools have already accelerated drug development, getting new treatments into clinical trials faster than ever. A notable example is an AI-designed drug candidate, INS018_055, which targets idiopathic pulmonary fibrosis, a chronic lung disease. By using deep learning and generative chemistry methods for drug discovery and design, researchers significantly accelerated nonclinical development and moved the drug through early clinical trials with promising safety and efficacy results.[35]

The regulatory approval process is guided by science; for pharmaceuticals, flexibility within the guidelines can allow the use of alternative approaches. For example, if no species can provide reliable, pharmacologically relevant safety and toxicity data, as is the case for some monoclonal antibody therapies, then a battery of *in vitro* tests can be used in combination to provide a weight of evidence approach prior to entering first in human trials. To date, this approach has only been used for a few biological drugs with well-defined and understood mechanisms of action. However, through actions developed in this plan, and by retrospective analysis of data from alternative methods together with *in vivo*-based data submissions, regulators can, and should, develop clear guidance to continue a flexible approach to the data submitted to support clinical trials. We expect the introduction of alternative approaches more widely into regulatory dossier packages will shorten

[35] https://www.fiercebiotech.com/medtech/insilico-medicine-begins-first-human-trial-its-ai-designed-drug-for-pulmonary-fibrosis; https://www.clinicaltrialsarena.com/news/insilico-medicine-ins018055-ai/

regulatory approval timelines. This will be monitored and reported publicly on an annual basis.

Box 4 – Alternative method-driven innovation in the biosciences

Researchers from the University of Cambridge have developed human primary liver cancer (PLC) organoids from three of the most common PLC subtypes: hepatocellular carcinoma (HCC), cholangiocarcinoma (CC) and combined HCC/CC (CHC) tumours. The team demonstrated the utility of this model system for drug screening, identifying the ERK inhibitor SCH772984 as a potential therapeutic agent for primary liver cancer. Overall, the pre-screening allowed the researchers to replace the use of almost 300 mice.[36]

Researchers from the University of Birmingham have developed the first mature bone organotypic model that accurately recapitulates human bone development and physiology. This includes a humanised bone organoid model to study the effects of unloading on bone remodelling that directly replaces the use of 110 rats in one user's lab. The model has also been applied in studies of bone endocrinology and mineral metabolism, replacing up to 30 rodents that would otherwise have been required.[37]

In a collaboration between NICEATM and the consumer products company Unilever, a skin sensitisation prediction tool (the Skin Sensitisation Risk Assessment – Integrated Chemical Environment - SARA-ICE) has been developed. SARA-ICE is a Bayesian statistical model, which estimates a human relevant metric of skin sensitiser potency that anyone can use. SARA-ICE uses existing *in vitro* and *in vivo* data from over 400 chemicals to make a prediction and illustrates the potential utility of a large data approach. The SARA-ICE model is now accepted as a defined approach in OECD Test Guideline 497.[38]

Researchers from the University of Oxford and pharmaceutical company Janssen have developed an *in silico* model that predicts the risk of drug-induced heart arrhythmias more accurately than animal studies. In an *in silico* drug trial, they tested 62 drugs and reference compounds at varying concentrations on a control population of 1,213 simulated human ventricular cells. Using software designed specifically for this purpose, they measured drug-induced changes in heart electrophysiology. The computer model demonstrated 89% accuracy in predicting the risk of drug-induced arrhythmias in humans, compared to up to 75% accuracy from previous animal studies.[39] This is an example of where human specific studies are better than animal use. We expect to see more such examples emerge and will expect early uptake of their use.

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36 Broutier, L *et al* (2017) Nat Med 23(12) 1424-1435 DOI: 10.1038/nm.4438

37 Finley, M *et al* (2023) F1000Research 12(357) DOI: 10.12688/f1000research.130779.1

38 https://www.oecd.org/en/publications/2023/07/guideline-no-497-defined-approaches-on-skin-sensitisation_30b1718f.html

39 Passini, E *et al* (2017) Front Physiol 8(668) DOI: 10.3389/fphys.2017.00668

Researchers from the University of Nottingham have developed non-animal-derived hydrogels to replace commonly used scaffolds that are derived from animals. These hydrogels have been used successfully for breast cancer cells, including both established cell lines and patient-derived samples, reducing the reliance on animal-derived scaffolds and the need for implantation into mice.[40]

Two species – a rodent (mouse or rat) and a non-rodent (dog, non-human primate or mini-pig) – are typically used as part of the drug development process to assess human safety and inform the design of human clinical trials. An NC3Rs-led data sharing project,[41] in collaboration with the Association of the British Pharmaceutical Industry (ABPI) and scientists from more than 30 global pharmaceutical companies and regulatory bodies, conducted a detailed analysis of toxicity testing data of 172 compounds and demonstrated opportunities to use one rather than two species for long-term toxicity studies in drug development. This has the potential to significantly reduce the use of second species testing in dogs and primates and provided the evidence base for the 'Virtual second species' CRACK IT Challenge.[42] Within current ICH guidelines it is possible under certain conditions to use a single species approach for biotechnology-derived drugs (e.g. biologicals), but this is not always applied. The NC3Rs has expanded its two species project to include detailed data on an additional 75 molecules – primarily small molecules – to build a stronger evidence base to support broader application of a single species approach across modalities. The MHRA will report annually on the impact the NC3Rs two species work has on regulatory dossier submissions containing second species data across differing modalities.

Barriers to the adoption of alternative methods

Despite the recognised scientific, economic and animal welfare benefits offered by alternative methods, barriers that limit their widescale adoption remain. These include:

- Lack of scientifically robust and validated alternative technologies that are sufficiently mature enough to replicate complex human biology for use in discovery research and acceptance by regulators.
- Funding of insufficient scale and duration to enable model development, qualification[43] and transfer between laboratories to overcome current scientific limitations.
- Lack of organisational and personal expertise, and access to specific technology or equipment.
- Lack of accessible case studies supporting cross-sector learning and best practice on risk assessments using alternative methods.
- Concerns about lack of support and acceptance from peers, scientific journals and regulators.

[40] Ashworth J *et al* (2020) Matrix Biology 85-86: 15-33. DOI:10.1016/j.matbio.2019.06.009

[41] https://nc3rs.org.uk/our-portfolio/review-use-two-species-regulatory-toxicology-studies

[42] https://nc3rs.org.uk/crackit/virtual-second-species

[43] A process by which an alternative method is demonstrated to be fit-for-purpose; and have sufficient reliability and rigor in a specific context of use to give confidence that decisions made based on data generated in these methods are robust. Qualification may also set expected criteria to be used in the subsequent validation.

- Poor knowledge about the availability of alternative methods and institutional commitment to *in vivo* models.
- Requirement for validation[44] and international agreement of testing methods and standards that need streamlining to allow timely regulatory acceptance.

Where alternative methods are to be used for regulatory testing purposes, they need to accurately model what will happen in a human body, relevant species or environment for the product under consideration. They need to be reliable, reproducible, and robust to provide reassurance on the safety of products before they are marketed, and so that decisions based on these methods are legally defensible. They do not need to show the same result as what might have been detected in an animal model, but they do need to show an appropriate level of predictive value for the intended use. This usually requires method validation which could involve interlaboratory testing to confirm consistency in specificity and sensitivity of the method between laboratories.

Companies and regulators have long faced a dilemma over who should take the lead in adopting alternative methods to generate data in drug and chemical development. Companies often wait for regulators to approve new approaches before investing in them, while regulators require strong evidence of reliability before updating guidelines. This has historically slowed progress. We want this to change and in recent years, there has been a shift towards greater collaboration, with both sides working together to change the regulatory framework. For example, the UK Regulatory Innovation Office is working closely with the Office for Life Sciences, MHRA and industry partners to support, develop and promote the use of advanced technologies in drug development to reduce animal use and improve predictive accuracy.

Through joint initiatives, workshops, and data-sharing, regulators and industry are now co-developing strategies to validate and integrate alternative methods, accelerating the transition towards non-animal testing. Key to this will be re-thinking the validation testing paradigms and strategies that operate today. Tiered or staged approaches could be employed to improve hazard identification and risk assessment. This would involve first curating and interrogating existing data sets to provide probabilistic models that enhance predictive accuracy prior to increasing the complexity and diversity of *in vitro* models. This approach is already being explored for chemical risk assessments. We will build on existing experience in this space and work with MHRA, Defra, EA, UKHSA and other relevant agencies to enhance approaches for medicines and environmental safety assessment.

The benefits to addressing these barriers are far reaching and go beyond replacing the use of animals. By leveraging the UK's strong science base, it is possible to derive economic benefits from the development of new models and tools which replace the use of animals in research, and in many cases, it will improve the accuracy and relevance of the science. The actions outlined in this plan will create a UK research system to deliver this by enhancing funding, fostering international collaboration, and strengthening regulatory support. By driving innovation and embedding cutting-edge non-animal technologies into research practices, the realisation of this plan will establish the UK as a global leader in alternative method adoption, delivering both scientific advancements and a meaningful cultural shift in animal use.

[44] A process by which an alternative method is demonstrated to consistently produce reliable results meeting pre-determined quality standards and acceptance criteria in a specific context of use. Validation of a test method is required for data generated in them to be accepted under the Mutual Acceptance of Data international Test Guidelines agreement, which supports international regulatory decision making.

Part II – The UK strategy for driving the use of alternatives to animals in science

Vision, Scope and Objectives

Our long-term vision is for **a world where the use of animals in science is eliminated in all but exceptional circumstances** achieved by creating **a research and innovation system that replaces animals with alternative methods wherever possible**. Recognising that UK law already requires that animals can only be used where no validated alternative exists, this strategy seeks to drive the creation of a wide range of new and validated alternatives used in discovery and translational research, and new approach methodologies used for chemical and environmental testing, and safety and toxicity testing of potential new human and veterinary medicines. This strategy lays out the steps we, the Government, will take over the next five years towards achieving this vision across the whole of the UK.

This science-led strategy is intended to cover the whole range of uses of animals in science, including for discovery, applied, translational, and regulatory research purposes. It recognises the importance of validation in enabling the ultimate adoption into practice of alternative methods, but also the need for effort, engagement and resources for model development and qualification, to establish their reliability and robustness. It specifically covers species protected under ASPA, recognising that this does not limit additional species from being protected as understanding of sentience evolves. It also does not preclude the development of alternatives to the use of animal species not covered by ASPA's protections (for example decapod crustaceans) or the use of products that have been derived from animals, but supports continued development, validation and use of animal-free reagents as they become available.

This vision is primarily aimed at the evidence-based **replacement** of animals in science, seeking wherever possible to remove the need to use animals entirely, especially those afforded additional protections under ASPA (e.g. non-human primates and dogs). However, **reduction** and **refinement** can also be enabled by alternative methods and the actions outlined in this plan will support all three 'Rs', even if replacement is the overall goal.

The plan has six objectives:

I. Accelerate the phasing out of animal use for research and testing through the replacement of animals in science.
II. Enable equivalent or better research and regulatory testing outcomes using alternative methods.
III. Partner with industry to increase private sector investment in development and adoption of alternative methods, driving economic growth.
IV. Improve national and international regulatory confidence in, and acceptance of, alternative methods, by working with regulators and scientists.
V. Create national infrastructure and collaboration frameworks to enable data-driven innovation and exchange to capitalise on our data assets.
VI. Promote the UK as a competitive world leader in alternative methods.

Our commitment to driving alternative method development and uptake in discovery research

The UK has a strong track record of nurturing and attracting the brightest minds and most innovative life sciences companies as a competitive and attractive destination for investment. Our world-class universities and institutes ensure the UK's position as a global hub of research, development and deployment. R&D also is essential to fulfilling this government's Plan for Change, improving lives across the UK and beyond.

The rapid pace of scientific and technological progress in alternative methods makes this a pivotal moment for change, offering significant opportunities to apply these innovations to fundamental research in human and animal biology, research which accounts for half of all regulated experimental procedures involving animals.[45]

However, challenges for development and the more widespread adoption of alternative methods in discovery research remain that impact the change of pace in practice. These are complex, stemming not only from the scientific and technical aspects of the research but also from broader cultural, societal and legal perspectives, which collectively delay their uptake. This is especially true given the plethora of alternative methods under development in academia and industry, all with slightly different set-ups, or delivering slightly different data, necessitating robust mechanisms for dissemination. This should be supported with transparent and accurate reporting of alternative methods experiments. Within this strategy, we are cognisant of the need for downstream regulators to ensure that human and environmental safety is their top priority, and that we should not delay the introduction of new and innovative products across all sectors, life enhancing medicines, vaccines and technologies.

The actions described throughout this plan will address the barriers concurrently to create the wider culture shift required to support the large-scale uptake of alternative methods to replace animal use and support the realisation of this plan's vision. More needs to be done to support specific co-ordination of alternative method development and its application to reduce animal use. This must be sustained over time to build the capability and capacity necessary in the skills base to drive the required culture shift. It must also consider method qualification to ensure robustness and reliability and lay the foundation for validation for regulatory testing purposes.

We will:

- **Create a preclinical translational models hub, supported by £30m of government funding.** By the end of 2026, we will establish a new institute to bring together data, AI, cell engineering, genomic technology and cutting-edge disease modelling capabilities to generate collaborative research at scale, including three fully integrated translational networks in key areas of health research. This will create a pipeline of novel translational medicine models, with opportunities for partnerships across academia and industry, ensuring increased productivity with fewer resources and less time wasted in development of therapies that are ineffective in humans. This will contribute to the UK's goal of becoming a global beacon for scientific discovery, boosting inward investment. We expect this translational hub to work very closely with academia and the life sciences industry, and we will also work with large AI companies to ensure that this makes use of the latest computational discoveries.

[45] https://www.gov.uk/government/statistics/scientific-procedures-on-living-animals-great-britain-2024

- **Increase investment in alternative methods**. We will focus an increased amount of government research funding specifically on the development and adoption of robust and well qualified alternative methods for discovery research. We will continue working with relevant government departments and UKRI to create and support further opportunities for investment in this strategic area, including through the NC3Rs, to continue funding innovation in the use of alternative methods for research and validation.
- **Enable funders to ensure thorough scrutiny of animal research in funding decisions.** UKRI has launched their new Policy on Research and Innovation Involving Animals,[46] and are already sharing policy, implementation and operational change plans with other funders to encourage policy changes for better embedding the 3Rs in the funding process. We will expect UKRI to give priority to research proposals that adopt appropriate human specific technologies. To enable this, we will work with funders (e.g. medical research charities, UKRI, and NC3Rs) to (i) create positive incentives for applicants to develop, validate and implement alternatives to animal use; and (ii) to empower reviewers and panels to support the phasing in of scientifically robust alternative methods where they exist, to promote the replacement of animals in research. Where appropriate, specific training, guidance and resources will be provided to support funding panels to make informed decisions on these elements of the application process.
- **Provide foundational training for early career researchers in alternative methods**. We will facilitate a generational shift in knowledge on the 3Rs and build capacity within the life sciences research base to recognise and deliver future reductions in animal use. Working with UKRI and NC3Rs, by the end of 2026 we will aim to offer 3Rs training to all PhD students and early career scientists who are embarking on careers using animals and alternative methods to create a workforce to match the UK's ambitions and respond to demands from the sector for expertise and skills in methods that do not use animals.
- **Publish areas of research interest for alternative methods.** Starting in 2026, we will publish biennially a list of alternative methods research and development priorities to coalesce UK scientists around these areas and to incentivise partnerships between research organisations, CROs and industry. These priority areas will be developed collaboratively between academic institutions, industry trade associations, learned societies, the NC3Rs Regulatory Sciences Forum,[47] the New Approaches to Chemical Risk Assessment in the Regulatory Space (NACRARs) Cross Government group, and international partners.
- **Strengthen the commitment of journal editors to publishing research using alternative methods.** Journals play a critical role in advancing science by disseminating high-quality, credible, and impactful research that drives innovation and shapes the future direction of science. Publishers and funders agree on the importance of alternative methods and are committed to work together more openly to promote their use. We will work with journal editors and publishers to ensure editorial policies incentivise well designed and reported alternative methods without requiring comparison with an animal model. Editors will provide guidance for peer reviewers on how to assess alternative method article submissions with an aim of encouraging the wider publication of non-animal methods and data. In tandem they will also develop metrics to quantify the number of animal and non-animal-based research articles published in their journals to monitor the effect these efforts have on submissions.

[46] https://www.ukri.org/news/ukri-wide-policy-on-research-and-innovation-involving-animals/

[47] https://nc3rs.org.uk/regulatory-sciences-forum

We will host a workshop with relevant stakeholders shortly to initiate this process and expect relevant recommendations to be published within the subsequent 12 months.

- **Increase the visibility of available alternative methods to facilitate their uptake.** The NC3Rs gateway[48] is a dedicated publishing platform for NC3Rs grant holders to report in detail their methodologies, helping to build confidence in 3Rs approaches and encourage their wider use. We will work with the NC3Rs to increase the scope of the gateway so that by the end of 2026 it is available to all researchers developing alternative methods, and work with government and public sector partners to support its use by the research and regulatory community.
- **Accelerate uptake in alternative methods through reform of animals in science regulation**. The Animals in Science Regulation Unit (ASRU) has already initiated their Regulatory Reform programme to improve performance and implement a new target operating model to meet the needs of an evolving scientific sector and regional partners such as Department of Health Northern Ireland. This work is due to be completed in 2025. We have commissioned the Animals in Science Committee (ASC) for advice on strengthening leading practice for the regulated sector and best practice for animal welfare and ethical review bodies (AWERBs). We will also commission the ASC to recommend corporate responsibility reporting expectations by establishments using animals on their use of alternatives. We will work with the Home Office to review how additional statistics such as those on the numbers of animals used for creation and breeding of genetically altered animals can lead to guidance on efficient breeding practices, or other replacement opportunities. Finally, by the end of 2026, we will complete full implementation of the Rawle Report recommendations, improving the approval processes around animal research and ensuring animals continue to only be used where there is no available alternative.

Our commitment to accelerating alternative methods validation and uptake for regulatory decision making

This government aims to position Britain as the best place in the world to innovate by ensuring safety, speeding up regulatory decisions and providing clear direction in line with our modern Industrial Strategy. Given the key role of regulators in driving the use of alternatives to animals, this strategy aims to ensure innovation and promote new opportunities for technologies through focused collaboration in the regulatory environment.

The adoption of alternative methods for regulatory decision making relies on their ability to generate data that effectively support efficacy, safety, hazard, and risk assessments – either complementing or fully replacing animal-based endpoints. To gain regulatory acceptance, these methods (on their own or in combination) must demonstrate reliability, reproducibility, and relevance, ensuring that the data produced are at least as robust and translatable as those from traditional animal models (without needing to mimic the results). Globally, efforts are underway to establish criteria that build confidence in alternative methods, ensuring they meet or exceed the standards of animal-based approaches. However, many regulations still mandate animal study data, with requirements varying across regions. For an alternative method to be accepted in regulatory decision-making, its applicability must be thoroughly evaluated in both chemical and biological contexts. This typically involves defining its scope before conducting interlaboratory validation studies to ensure a method is fit for purpose, as outlined by the OECD.

[48] https://f1000research.com/nc3rs

Traditional approaches to validation are often linear, stepwise, and can be a long and resource-intensive process. We recognise this as a potential block to change. Establishing confidence in modern testing paradigms, where different alternative methods may be integrated to replace an existing animal test, requires a different approach. Considerable effort is being invested globally to address this, building upon next generation risk assessment approaches proposed for chemicals testing. There is a global network of centres established to validate alternative methods (the International Cooperation on Alternative Test Methods (ICATM)), in which the UK is engaged, though with limited national coordination of validation efforts and no current dedicated laboratory capacity.

Establishing a cohesive research community focused on animal replacement requires greater awareness of what alternative methods are in development, already exist and are validated, and what the priorities are for end users. More could be done to facilitate early engagement, training and knowledge sharing across bioscience communities to build confidence in alternative methods and accelerate their application. This needs to be from the start and throughout the development of a method, to increase the likelihood of a given method being deployed by companies and regulators to support decision making.

We will:

- **Establish a UK Centre for the Validation of Alternative Methods (UKCVAM)** to drive UK validation efforts necessary to accelerate both industry confidence and regulatory acceptance. It will take the form of a ‘hub and spokes’ model and will provide a vital bridge between scientific innovation and regulatory uptake, accelerating the transition of alternative methods out of the lab and into tools regulators can trust for human relevant decision making. The hub will establish governance and oversight and provide an independent perspective on the standardisation and validation of methods, training, and coordination of a network of UK laboratories to carry out robust and consistent validation studies. The new Centre will provide a focus for the UK in international validation programmes to ensure that validated alternative methods are recognised across borders. The network (the ‘spokes’) will deliver the studies defined by the UKCVAM and participate in developing, curating and disseminating standardised protocols, and where considered suitable, explore international interlaboratory ring trials or innovative ways of agreeing regulatory readiness. Network members will come from the large number of well equipped, but decentralised, laboratories that are managed and run by highly trained staff with significant technical expertise that exists within the UK’s thriving CRO sector, government research departments, industry, and universities and research institutes. This approach will provide the necessary sector- and technology platform-specific expertise required to validate effectively the breadth of alternative method technologies for their wide-ranging applications. The UKCVAM will provide the necessary support to regulators to apply the most scientifically relevant tools and technologies for enhanced regulatory decision making without animals and enable a systemic advance in the rate of change in the UK regulatory culture.
- **Publish regulatory agency accepted alternative methods and priorities for future development and validation.** We will work with UK regulators (e.g. MHRA, FSA, EA, HSE, VMD) to publish in 2026, and then biennially, (i) a coherent list of alternative methods that would be acceptable data sources, and (ii) a list of regulatory priorities for alternative methods to help guide investment for development, qualification and validation accelerating the regulatory acceptance of alternative methods. These will be published as part of the UK areas of research and testing interest in alternative methods. An initial list of priorities for targeted replacement is provided in Part III.

- **Expand challenge-led innovation for alternative methods.** We will run increased challenge-led innovation funding schemes to deliver both the alternative methods priorities for (i) development and (ii) qualification/validation published as part of the UK areas of research interest in alternative methods. The latter will be delivered through new 'Validation Accelerator grants' to push promising alternative methods along the validation pipeline. Focusing on real-world biological problems defined and informed by industry and regulators, and publishing these validated methods endorsed by regulatory authorities, will give end-users (including chemicals and pharmaceutical companies) the confidence needed to drive widespread uptake and acceptance. The first round of grants will be awarded in 2026.
- **Support training in alternative method development, qualification and validation.** We will work collaboratively with life sciences organisations, trade associations, learned societies and research funders to support ongoing continued professional development of their members in this rapidly evolving field to better fill skills gaps where they exist. We will provide opportunities for specific training to drive qualification of alternative methods (ensuring robustness and reproducibility) and regulatory validation. These activities will be advised by the OECD UK National Coordinators and NACRAS, and facilitated by the NC3Rs Regulatory Sciences Forum and UKCVAM that could enable training and placements.
- **Supporting the upskilling of regulatory assessors**. To ensure regulators stay at the forefront of innovation in efficacy, safety and risk assessments, they will receive training either directly (e.g. through established programmes such as those offered by the Cosmetics, Toiletry and Perfumery Association and the pharmaceutical industry IQ consortium) or through secondments facilitated through alternative methods developers, academic institutions, and life-sciences companies, such as CROs, that develop and share these services. Regulators will be funded to attend scientific meetings and hands-on workshops to engage directly with method developers and industry leaders to help bridge gaps in understanding and address perceived regulatory barriers to implementation. Working with the Regulatory Sciences Forum, by the end of 2026, we will have identified all existing regulatory training opportunities and created new ones to address any gaps, ensuring that all regulators consistently achieve and maintain the necessary competencies to evaluate alternative methods as they evolve and to effectively apply data generated in them for regulatory decision-making.
- **Develop mechanisms to enable regulators to provide pre-submission feedback.** We will create mechanisms for regulators to engage with companies on the application of alternative methods during the product development process and prior to regulatory dossier submission, ensuring that regulators are sufficiently resourced as not to be overwhelmed by this process. This will expedite the inclusion of alternative methods, potentially complementing standard *in vivo* data to build confidence, and raise the visibility and acceptance of scientifically robust non-animal testing strategies. For example, this could be through the increased uptake of the MHRA's scientific advice service,[49] and be similar in practice to the EMA's Innovation Task Force, the European Chemicals Agency Examination of Testing Proposals process,[50] and the U.S. FDA's Innovative Science and Technology Approaches for New Drugs program. MHRA will also publish a statement to signal internally at the agency and to wider industry its approach regarding submissions using only alternative methods. We will assess the impact of this by collating and publishing annually the number of meetings with

[49] https://www.gov.uk/guidance/medicines-get-scientific-advice-from-mhra

[50] https://echa.europa.eu/regulations/reach/evaluation/examination-of-testing-proposals#:~:text=ECHA%20examines%20(according%20to%20Article,the%20use%20of%20vertebrate%20animals.

regulators, and case studies, focused on the use of alternative methods to support regulatory submissions and how this has impacted regulatory approval timelines. We will start this process in 2026 by generating the baseline data from which future comparisons can be made. We will work with other regulators to issue similar public statements supporting the acceptance of alternative methods and to create incentives that encourage companies to develop and use them.

- **We will quantify annually the inclusion of second species testing in clinical trial applications.** We will work with MHRA and NC3Rs to review the impact of NC3Rs' work to support single species testing by collecting data annually on the number of clinical trial applications that include toxicity tests conducted in two species. This will be reported publicly in the KPIs dashboard.

Our commitment to delivering the transformative potential of our data assets.

Data is the DNA of modern life and drives every aspect of our society and economy. The UK has emerged as a leading hub for data and AI in the life sciences, fostering a vibrant ecosystem focused on data-driven solutions in health and biotechnology. Companies such as DeepMind, Isomorphic Labs, Recursion (through their merger with Exscientia), Healx, PharosAI, Optibrium and Oxford Nanopore Technologies are developing cutting-edge approaches that leverage AI to enhance drug discovery, diagnostics, and personalised medicine. The UK data economy is predicted to contribute £200 billion or 10% of UK GDP by 2030,[51] with the life sciences sector contributing significantly to this total, as it increasingly integrates AI to make the most of existing data rather than generate data from new animal studies and drive efficiency, innovation, and competitiveness in a rapidly evolving landscape.

The potential of existing academic and industrial data to inform discovery, translational, and regulatory research is vast, offering a pathway to significantly reduce our reliance on animal testing. High-throughput sequencing technologies and sophisticated imaging techniques have enabled the collection of extensive datasets that reveal intricate biological processes at unprecedented resolution. AI has further accelerated data analysis, allowing researchers to uncover patterns and insights that were previously unattainable.

Our academic research funders, including UKRI and the NC3Rs, have begun to invest considerably in data sciences and the infrastructure required to maximise the transformative potential and animal replacement possibilities AI offers. The NC3Rs has demonstrated over the last 20 years how its role as a trusted intermediary has empowered companies to share precompetitive data safely and collaboratively, driving innovations that reduce reliance on animal testing. In the 2025 spending review, we committed £8 million from DSIT's new Sovereign AI Unit to OpenBind, a consortium using experimental data technology to build the world's largest dataset on drug–protein interactions to accelerate drug discovery.

Data sciences and AI are increasingly being applied as alternative methods across the pharmaceutical, agrichemical, consumer products, and chemicals sectors to streamline research and development processes and enhance product safety and efficacy. In pharmaceuticals, these tools facilitate drug discovery by analysing vast datasets to identify potential therapeutic targets and predict drug interactions, significantly reducing the need for animal testing in early-stage evaluations. Similarly, in the hazard-driven assessment of

[51] https://www.pwc.co.uk/economic-services/assets/ai-uk-report-v2.pdf

industrial and agrochemicals, AI presents valuable opportunities to enhance risk-based approaches by incorporating exposure assessments, thereby improving ecotoxicology and human health testing.

Leveraging data from various sources, including genomics, proteomics, nonclinical studies, clinical trials and environmental studies can accelerate the pace of discovery, streamline drug development and ensure regulatory compliance while prioritising animal welfare. Regulatory agencies globally are actively exploring the opportunities and challenges presented by rapid advances in AI and data sciences. The U.S. FDA has launched the AI4Tox programme[52] to support their integration of AI within safety assessment practices. The EMA has created an AI workplan[53] that outlines their vision for AI across drug development, and the MHRA has published a policy paper on the impact of AI on medicines regulation.[54] Furthermore, UKRI has recently established the UKs first Centre of Excellence on *In silico* Regulatory Science and Innovation (CEiRSI) to work with the MHRA, FDA and EMA in developing digital tools for faster and more efficient drug and medical device development and testing.[55] In other sectors, the HSE has published their regulatory approach to AI and how it impacts their role in protecting people and places, including chemicals and pesticides regulation.[56]

The UK is leading the way in many areas of data-driven research, but significant challenges exist which may temper this progress. Issues surrounding data quality, standardisation and interoperability persist, limiting the seamless integration of diverse datasets. Access to high-quality data remains restricted, and existing regulatory frameworks often do not facilitate the efficient use of AI technologies. Furthermore, limitations in how advanced computational technologies and methodologies are being exploited, coupled with the relative state of maturity of the biological data landscape, pose hurdles that could slow the pace of advancement. Overcoming some of these hurdles may require re-defining how dialogue between companies and regulators occurs, and building upon existing industry resources. One example, the ReFRAME.org database offers a strategic advantage for industry and policy leaders by streamlining drug development pipelines; its extensive catalogue of >12000 clinically tested compounds enables faster repurposing, reduces research and development costs, and aligns with regulatory goals for more efficient innovation, enabling common biomarkers and key molecular events to be assessed, without the need for new animal studies. Safe spaces to foster confidential data sharing with regulators to discuss the potential acceptability of specific methods for a given endpoint, and a regulatory sandbox, providing a forum where method developers and regulators can discuss general regulatory need and solutions may be required to drive change in this area. In addition, the government recently announced £600m in partnership with Wellcome to create a Health Data Research Service that will revolutionise health data access for research in the UK. We are also home to the European Bioinformatic Institute and OpenSAFELY, a programme of data sharing that allows better use of data to identify better targets for new drugs.

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52 https://www.fda.gov/about-fda/nctr-research-focus-areas/artificial-intelligence

53 https://www.ema.europa.eu/en/news/artificial-intelligence-workplan-guide-use-ai-medicines-regulation

54 https://www.gov.uk/government/publications/impact-of-ai-on-the-regulation-of-medical-products

55 https://www.manchester.ac.uk/about/news/uks-first-in-silico-regulatory-science-and-innovation-centre-of-excellence-gets-green-light/

56 https://www.hse.gov.uk/news/hse-ai.htm

We will:

- **Increase investment in data-driven biology:** We will work with relevant government departments, UKRI, NC3Rs and other funders to increase research funding in data-driven biology. This will include supporting the development of computational technologies, methodologies and resources that leverage existing biological data and emerging bioanalytical or biological-based technologies to derive new biological insights and knowledge without using animals. The government is funding collaboration between business and the UK's world-class universities to develop new AI courses, launch new AI fellowships and establish a new AI talent scholarship and we will ensure this investment includes animal alternatives work where appropriate. This is exemplified by the £6.2 million invested across seven CERSIs, and the £8 million committed in the 2025 spending review to support OpenBind, to help drive advancements in healthcare. This pioneering use of AI could cut the time it takes to bring life-saving treatments to patients and represents just one example of innovation being championed by the UK's seven new regulatory science powerhouses.
- **Establish data sharing frameworks to support the equitable access to public and private data sources**: We will work with data controllers, companies and academics to better understand the barriers within the sector to sharing data. We will use this knowledge to explore creating an accessible data resource for development and training of predictive models (e.g. for toxicology), allowing fewer animals for regulatory submissions. This could take the form of 'data trusts' and/or federated models such as those explored in the pharmaceutical sector through the Innovative Health Initiative-funded MELLODDY[57] and FACILITATE[58] consortiums. Companies will be expected to provide their data to such a safe harbour resource. This will be supported by actions that look to improve how data is used, maintained and shared across the economy, including investing up to £12m in UK Data Sharing Infrastructure initiatives. Working with partners across Government, including the National Data Library (NDL) and the AI Opportunities Action Plan, we will identify up to five relevant high impact data sets to make available to AI researchers and innovators.
- **Enhance data curation and quality control and develop regulatory frameworks for data use**: The existence of data across multiple sites, in multiple formats and with potentially different definitions and standards presents a challenge for application of AI. We will establish and implement standardised protocols for data collection, curation, and quality assessment to address these challenges, and enhance data interoperability to ensure that relevant datasets are reliable and suitable for reuse. We will focus initial efforts in toxicology and safety assessment as across pharmaceuticals, (agro-) chemicals, medical devices and consumer products there is a vast amount of this data locked in inconsistent, siloed formats, preventing their wider use in the development and training of AI models. We will engage with data controllers and scientists to assess the utility of existing data principles to inform this work. Furthermore, we will collaborate with regulatory agencies to develop guidance and best practice that aligns with the AI Opportunities Action Plan, and which recognise and incentivise the use of existing high-quality data and accelerates AI adoption in medicines approval and in ensuring the safety of chemicals and the environment. We will use our existing partnerships with global regulatory organisations so that our efforts align internationally to support harmonisation and accelerate global acceptance. We will establish pro-innovation

[57] The MELLODDY project aims to establish an AI platform that would make it possible to learn from multiple sets of proprietary data while respecting their highly confidential nature: https://www.ihi.europa.eu/projects-results/project-factsheets/melloddy

[58] The aim of FACILITATE is to develop a prototype of a patient-centered, data-driven process that would allow innovative data sharing and the re-use and return of clinical trial data to study participants: https://www.ihi.europa.eu/projects-results/project-factsheets/facilitate.

initiatives such as regulatory sandboxes to work with regulators to identify their future AI capability needs and support them to scale up their existing AI capabilities. This will include launching a strategic secondment program, embedding regulatory staff into data science organisations and vice versa. This initiative will equip regulators with the expertise to interpret AI-generated data, ensuring informed, forward-thinking regulatory decisions that keep pace with technological advancements.

Our commitment to international leadership and cooperation

The use of animals in science is an international matter with researchers across the globe collaborating, publishing and reviewing each other's work. Pharmaceutical, agrochemical and chemical companies often have global footprints and interact with many different regulators and government agencies, depending upon the need to register a new product. These companies are often represented or supported by industry bodies such as the ABPI, European Federation of Pharmaceutical Industries and Associations, CropLife UK, National Office for Animal Health, and the European Partnership for Alternatives to Animal Testing to provide a coherent voice on the international stage, especially when regulatory guidelines require development and revision. This is particularly visible as the development of strategies on alternative methods has started to evolve.

This strategy will build upon those being developed in the EU and U.S. In April 2025, the FDA published a high-level roadmap to phase out animal testing for the development of drugs based upon monoclonal antibodies, and in May 2025 the NIH indicated that they were to prioritise funding for human based research technologies. The European Commission is also developing a roadmap to phase out animal testing for chemical safety assessment and is due to publish by the end of Q1 2026. The details behind these other international initiatives, and particularly the implementation strategies, are yet to be defined. It is therefore expected that the international landscape to phase in alternatives, and phase out animals, will evolve in a co-ordinated manner across the UK, EU and U.S. as stakeholders agree the priority areas for implementation of these individual, yet inter-linked, initiatives.

Many of the tests used for chemical and drug safety regulations are based on international agreements (e.g. they have been adopted as OECD Test Guidelines or incorporated within ICH/VICH Guidelines or ISO standards) and companies are unlikely to use different methods to register their products for use in the UK if the data will not be accepted by other jurisdictions. Aligning newly developed tests through OECD/ICH would prevent the need to repeat efforts with unaligned methods, which is a costly and inefficient undertaking. Furthermore, the OECD Guidelines for the testing of chemicals are often used to fulfil standard information requirements (SIR) set out in REACH. UK REACH registrants must fulfil these SIRs depending on the quantity of the substance that is manufactured or imported.

The UK is determined to provide responsible global leadership in tackling world challenges. We play a key role in international regulations and standards involving animals in science and lead on many alternative method projects with respect to development, review and drafting of guidance. Agencies such as the FSA are an active member of Accelerating the Pace of Chemical Risk Assessment, an international collaboration that brings together government entities to drive innovation in chemical risk assessment. Reliable and reproducible data are essential to support the OECD's Mutual Acceptance of Data principle ensuring that studies following OECD Test Guidelines and Good Laboratory Practice are trusted across member countries. Regulatory authorities receiving such data

know that accepted quality and scientific standards were followed, and they do not have to re-evaluate a test protocol to determine its robustness.

Several other countries and multinational organisations are increasing their support for alternative methods, including the EPAA, PARC, FDA, EMA, the European Commission and the U.S. National Institutes of Health. Many of these are national or EU-led programmes and so UK participation in them is currently limited. However, through this plan, we hope to increase these opportunities. Nevertheless, as contributors to EU Horizon, the UK has collaborative opportunities with many of our key neighbours.

UK regulatory agency connectivity and cooperation with global counterparts is particularly strong where alternative methods discussions are happening around chemicals, plant protection products and foodstuffs. However, as the regulatory landscape for defining and including alternative methods in medicinal product development evolves, there is a unique opportunity for the MHRA to have a strong voice. We will develop close relationships with countries where our interests align to drive international acceptance, seeking to showcase successful approaches to enable alternative method uptake across the world.

We will:

- **Establish the UK as a global leader in the regulation and science of alternative methods**. The Government will ensure that the UK provides clear leadership and direction on key forums and international committees relevant to this space (for example ICH, VICH, OECD, ISO, ICATM and the International Medical Device Regulators Forum) and that this is coordinated and led by the most appropriate expertise and organisations. The UK will also continue to develop bilateral partnerships with the U.S., EU, Switzerland, Japan, Australia and Canada and explore interest in Singapore, to share knowledge and expertise on alternative methods and agree joint projects on development and validation. By the end of 2026 we will have advanced our efforts for the MHRA to be a member of the International Medicines Regulator's Working Group on 3Rs, working collaboratively with EMA, the Swiss Agency for Therapeutic Products, the Japanese Pharmaceuticals and Medical Devices Agency, the Australian Therapeutic Goods Administration, Health Canada, and the FDA to support greater harmonisation in the use of alternative methods in nonclinical testing. We will also advocate for alternative methods to be discussed at the G7 so that actions in this space can be coordinated across these countries. We will work closely with relevant EU institutions to ensure alignment between the UK's ambitions and the EU roadmap.[59]
- **Launch specific projects to secure international acceptance.** UKCVAM, working with the NC3Rs Regulatory Sciences Forum, OECD UK National Coordinators, and NACRARS will drive specific UK-backed programmes to ensure the generation of data necessary for international acceptance, in line with regulatory priorities.
- **Host an international meeting of regulators in the UK on the validation and acceptance of alternative models**. We will bring together regulators from across sectors globally to agree actions that will incentivise and speed up the validation and acceptance of alternative models.

[59] European Commission Roadmap towards phasing out animal testing: https://single-market-economy.ec.europa.eu/sectors/chemicals/reach/roadmap-towards-phasing-out-animal-testing_en

Our commitment to effective governance culture

The use of animals in science, and in their replacement, is of interest to a wide variety of government departments and bodies. The Home Office has responsibility for overseeing compliance with ASPA. The Department for Science, Innovation and Technology (DSIT) has oversight of the UK research system in general and the development of alternative methods in particular. Defra is responsible for environmental protection, protection of the health and welfare of animals, and for UK REACH and pesticides regulations; and the Department for Health and Social Care (DHSC) has an interest in medicines safety and development, and public health. In addition, there are many regulatory and advisory bodies with responsibilities in the above remits, including Cefas, EA, FSA, HSE, MHRA, VMD and UKHSA; research funders such as the NC3Rs, and UKRI; alongside ethical review bodies sitting within research organisations.

Advice on the use of animals in science, in the context of ASPA, is provided to government by the ASC. The ASC is responsible for providing independent impartial, balanced and objective advice to the Home Office and to the Northern Ireland Department of Health on issues relating to the ASPA and its functions under it. The ASC is also responsible for advising, promoting and sharing good practice with, and between, AWERBs in the UK. The ASC was established under ASPA in 1986 and strengthened in an amended ASPA in January 2013, and is an independent, non-executive advisory Non-Departmental Public Body. There are also several scientific advisory committees across departments such as the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment, which use chemical safety data to advise government on regulatory decisions. The experts within these committees are a valuable resource with relevant expertise and will be involved in future activities.

In the chemical safety area, the FSA established NACRARS in 2022 as a Cross Government Strategic Steering Group on new approach methodologies. The NACRARS group encourages discussion and partnerships that will be instrumental in creating confidence in the use of new approach methodologies in chemical risk assessment amongst regulators.

Driving the development of alternatives to the use of animals in science requires better coordination across the complex landscape involving a diversity of knowledgeable stakeholder groups across science, regulatory, welfare and wider society. In this strategy, the Government is taking the opportunity to align the system around the vision outlined here to foster clear oversight and ministerial drive to increase use of alternative methods.

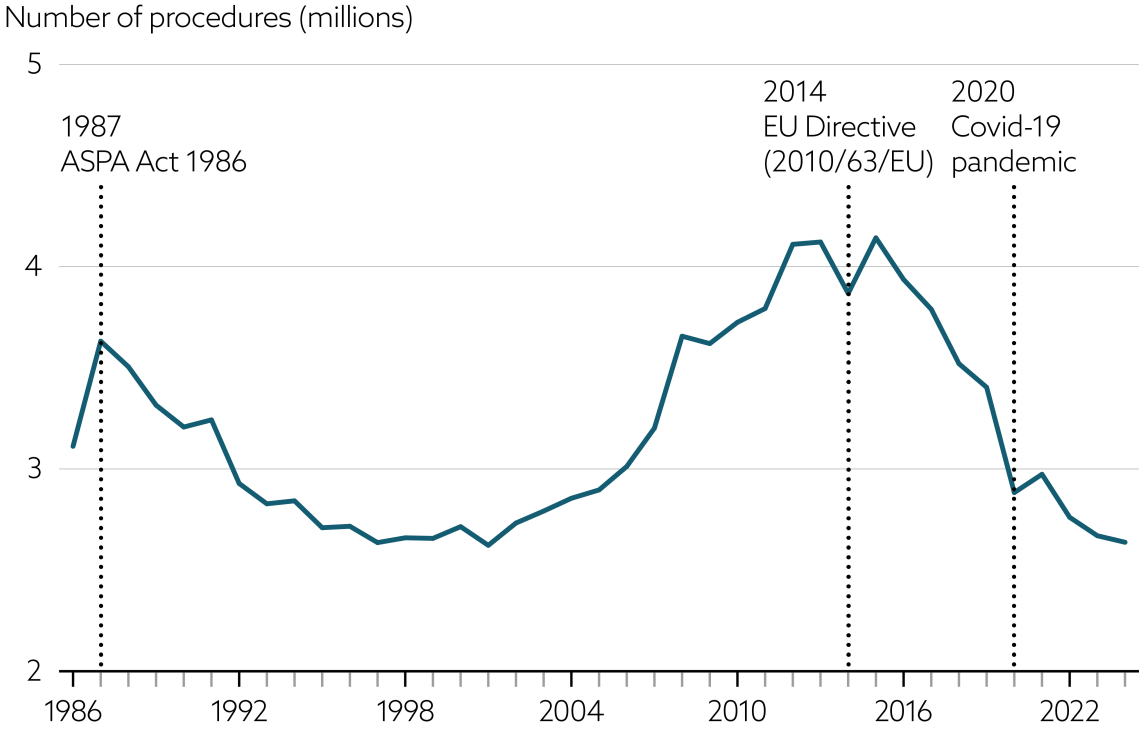
We will:

- **Provide Ministerial leadership on alternative methods**. A cross-government Ministerial committee, chaired by the Science Minister and including, but not limited to, representatives of key departments (DSIT, Home Office, DHSC, Defra, Department for Business and Trade, MOD), regulators, funders and the Chair of the ASC, will be formed in 2026 and will meet regularly to drive delivery of this plan. The group will be supported by an Alternative Methods Strategy Delivery Group, chaired by officials from DSIT, with representatives from all interested departments and government bodies. We will also work closely with the Regulatory Innovation Office to ensure our work with regulators in this area aligns with our missions and the modern industrial strategy.
- **Formally involve DSIT in the direct commissioning and receipt of advice from the ASC**. Currently the ASC directly advises the Home Office, however responsibilities around alternative methods fall to DSIT. Ministers from the Home Office and DSIT will

in future jointly commission the ASC and the relevant DSIT minister will receive advice on the implementation of this plan.

- **Enable better advice on alternative methods.** We will establish an alternative methods committee, overseen by the ASC, that will provide independent impartial, balanced and objective advice on alternative methods. The committee will comprise representatives from academia, industry, CROs, NC3Rs and other relevant stakeholders with expertise in the development and application of alternative methods specifically to reduce animal use and ensure animals are only used where no alternative is available.
- **Restart the survey on public attitudes to animal research.** This survey was carried out regularly until 2018 but ceased during the pandemic and has not been restarted. We will restart the survey in 2026 and run it every two years to ensure that the government, policymakers, companies and civil society organisations have a shared understanding of public opinion on the use of animals in science.
- **Establish key performance indicators (KPIs) with which to assess the delivery of this strategy.** Through the Alternative Methods Strategy Delivery Group we will develop and publish a set of qualitative and quantitative KPIs in 2026 to measure how successful we have been in delivering the objectives described within this strategy. We will create a publicly available dashboard of progress against key deliverables.

Figure 1: Total scientific procedures in Great Britain, 1986 to 2024

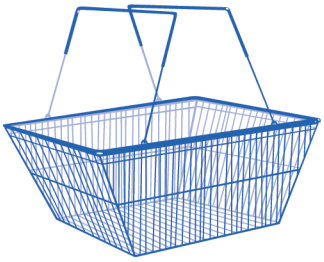


Source: Home Office, Annual statistics of scientific procedures on living animals, Great Britain 2024: data tables, table 1.1 and table 12.

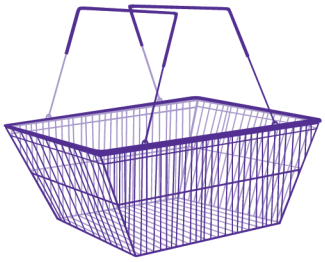
Part III – Priorities for targeted replacement of animal tests

There are considerable opportunities to replace certain animal uses with scientifically robust and validated alternative methods both immediately and over the longer term. A clear understanding of which animal-based approaches are ready for replacement, and which require further development and investment, is critical to ensure targeted efforts and appropriate resource allocation.

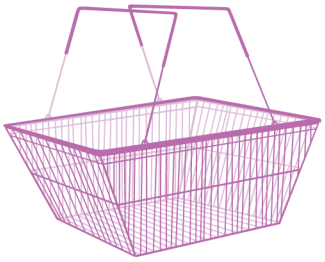
In line with international practice, we will use the '3 baskets'[60] approach to group animal tests, providing a structured basis for identifying priorities and informing decisions on where support is most urgently needed.



Basket 1:
Animal testing/models for which mature replacement technologies already exist and could be applied to phase out in all but exceptional circumstances.



Basket 2:
Animal testing/models for which viable alternative methods could be developed/adopted in the medium term.



Basket 2:
Animal testing/models that focus on more complex endpoints and for which alternative methods are longer term aims.

Below is an initial list of animal tests or methods in each category, alongside proposed targets to accelerate their replacement. These have been agreed with the relevant regulatory bodies in the UK and we will continue to work with other jurisdictions to accelerate global harmonisation of these approaches. This list is not exhaustive and will be reviewed and refined on a regular basis. Full details will be included in the UK alternative method priorities published later this year, and biennially, in consultation with the life sciences community. This will consider both discovery research and regulatory testing priorities.

As the scientific and technological maturity of alternative approaches progresses, it is expected that models will move from basket 3 to basket 2, and eventually to basket 1.

[60] Adapted from similar EFPIA and European Commission activities.

Basket 1 – Tests with potential for rapid transition to non-animal methods

This basket describes animal testing or models for which mature replacement technologies already exist. New legislation or revisions to guidelines or the British Pharmacopoeia could achieve a phase out of these tests in all but exceptional circumstances.[61]

1. Replacing the rabbit pyrogen test

Pyrogens are fever-inducing contaminants that may unintentionally be present in medicines administered by injection (including vaccines, blood products, radiopharmaceuticals, antibiotics and large volume solutions for infusion). Their detection is essential to ensure that medicines administered by this route are safe. For decades, the rabbit pyrogen test (RPT) has been the traditional method. In this test, a small amount of the product is injected into rabbits, and their body temperature is monitored. If the rabbits exhibit a fever, it indicates the presence of pyrogens in the product.

Driven by MHRA scientists, the *in vitro* Monocyte Activation Test (MAT) has been developed as an alternative cell-based assay to detect and quantify endotoxin and non-endotoxin pyrogen contaminations. The assay employs human peripheral blood mononuclear cells to mimic the human immune response by measuring cytokine production induced in response to pyrogens.

The European Pharmacopoeia, a supranational pharmacopoeia brought into force through publication in the UK national British Pharmacopoeia, as of July 2025 removed the RPT from all of its official standards. We will work with UK regulatory agencies to accelerate the replacement of the RPT with the MAT in other UK guidelines.

Target: By the end of 2025 we will aim to apply only validated alternative methods for pharmacopoeial pyrogen testing.

2. Replacing adventitious agent testing in animals

Adventitious agents are contaminating microorganisms (e.g. viruses, bacteria, mycoplasma and fungi) which have been unintentionally introduced during the manufacturing process of biological products (vaccines, cell substrates, and biopharmaceuticals). The highest risks are associated with raw materials of biological origin, like serum, and during viral amplification within a bioreactor. The *in vivo* adventitious agent test is performed by inoculating the test sample into animals (adult mice, suckling mice, guinea pigs, embryonated chicken eggs) and observing them for evidence of viral infection for a defined number of days.

There is general international acknowledgement that the *in vivo* adventitious agent tests can be replaced with molecular methods including polymerase chain reaction (PCR) and next generation sequencing (NGS) with targeted (to specific genes, coding regions or chromosomal segments) or non-targeted detection. These approaches have important

[61] If a validated alternative approach exists that provides the same level of regulatory confidence in safety testing as using an animal model, then ASPA mandates the use of the alternative approach. Where other countries do not accept the use of alternative approaches, *in vivo* tests may still need to be conducted to satisfy global regulatory requirements.

advantages including higher sensitivity and selectivity, and increased breadth of detection, especially when using a non-targeted approach. The ICH Q5A guideline, used worldwide as a reference for viral safety, has been recently revised to integrate NGS approaches.

A lack of international harmonisation and acceptance of these approaches, and confidence in their utility by some manufacturers is hindering their wider adoption. In collaboration with UK regulators, we will strengthen UK guidance on adventitious agents testing to make clear that alternative methods must be considered as the first option. We will also work with manufacturers and global regulators to promote broader acceptance of non-animal approaches by sharing best practices, data and experience, helping to accelerate the global transition to non-animal methods.

Target: We will aim to apply only validated alternative methods for pharmacopoeial adventitious agent testing for human medicinal products licensed in the UK by the end of 2027.

3. Phasing out preclinical animal testing of biologicals where no pharmacologically relevant animal models exist

Therapeutic monoclonal antibodies are an increasingly important type of immunotherapy. They are part of a group of medicines called ‘biologicals’ because they are produced from living organisms (including bacteria, yeast, and plant, or animal cells), rather than being synthesised chemically. Because of this, they are able to target specific cells or molecules with high selectivity and potency, triggering an immune response, which in cancer therapy, for instance, can lead to the death of tumour cells.

Most new chemical drugs are tested in rodents and non-rodents prior to human trials. However, because antibodies and some other peptide drugs are often specific to human targets and may not interact meaningfully with animal systems, traditional animal testing for such drugs is not relevant. In the case of several therapeutic biologicals, development and authorisation has used either one animal species, or none at all. In these latter cases, developers have used a suite of *in vitro* assays together to provide a weight of evidence approach to assure safety and satisfy regulatory guidance.

Regulatory authorities in the UK, U.S., EU and Australia have all approved clinical trials of biological therapies without the use of standard preclinical animal data packages. These approvals have been made on a case-by-case basis for each product where the safety profile was anticipated to be acceptable, the *in vitro* data provided had been generated using validated and robust methods, and a robust clinical biomarker monitoring program based on validated safety biomarkers had been established.

Currently, there is no international regulatory guidance that explicitly permits only the use of non-animal data to support clinical trial applications. Decisions are made on a case-by-case basis by each regulatory authority based upon the scientific justification and relevance of the data submitted. However, the U.S. FDA has in 2025 announced plans to phase out animal testing for monoclonal antibodies using a range of alternative methods, including AI-based computational models, cell lines, and organoid toxicity testing.

Target: The UK currently applies this type of judgement in practice for biologicals where there are no relevant animal species, but will move to formalise this. By the end of 2026 we will define and apply guidance that permits first in human clinical trial submission for biological therapies where no pharmacologically relevant preclinical animal model exists based only on non-animal data.

4. Replacing *in vivo* skin irritation testing

Skin irritation testing is required before registering medical devices, chemicals and medicines to assess whether exposure to a substance or mixture causes reversible damage to the skin. Traditional *in vivo* skin irritation tests, like the Draize test, involve applying a chemical directly to the skin of animals, often rabbits, and observing for signs of irritation such as redness, swelling or skin damage over time. Based on these signs, the substance is classified as an irritant or not.

An *in vitro* skin irritation assay using reconstructed human epidermis (RhE), which mimics the structure and function of human skin, has been designed to determine if a substance may cause skin irritation, especially for non-corrosive substances, without the need for animals. The test measures cell viability, to determine the extent to which a substance induces cell damage.

The use of animals for skin irritation testing has largely been replaced by a validated alternative method described in OECD Test Guideline 439. This guideline also includes a set of performance standards to assess similar or modified RhE-based tests. There are currently three validated test methods that adhere to this guideline.

Target: By the end of 2026 we will aim to apply only validated alternative methods to satisfy UK regulatory requirements for skin irritation testing.

5. Replacing animals used for eye irritation testing

Eye irritation testing is required before registering chemicals, medicines, medical devices and biocides to assess if changes to the eye caused by a specific substance can be fully reversed. Traditionally, *in vivo* testing involves applying a substance directly to the eyes of animals, usually rabbits, and observing them over time for signs of irritation or damage to eye cells.

There are nine non-animal OECD test methods available to assess the potential of substances to be hazardous to the eye and which focus on understanding the mode of action(s) leading to cell damage. Each method is considered reliable and valid under different conditions (known as applicability domains) and can be used to identify different categories of irritation/damage, for example whether this is reversible or irreversible. Currently, only two OECD test methods (OECD 492B and OECD 467) can fully identify all categories of eye hazard.

The OECD has developed a guidance document - OECD GD 263: Integrated Approaches to Testing and Assessment (IATA) for Serious Eye Damage and Eye Irritation – to help end-users decide how to use the test methods that can only partially identify ocular

hazards and cannot be used as standalone test methods. This document explains how *in vitro* test results can be used alone or in combination as part of a tiered testing strategy.

Target: By the end of 2026 we will aim to apply only validated alternative methods to satisfy UK regulatory requirements for eye irritation testing.

6. Replacing animal use in skin sensitisation testing

Repeated exposure to a substance or chemical able to elicit an allergic response in susceptible individuals can lead to a condition known as allergic contact dermatitis. Skin sensitisation testing is used to identify these substances and is a regulatory requirement for all chemicals, medicines, and medical devices prior to their approval and registration. Until recently skin sensitisation testing relied on animal-based tests in guinea pigs and mice.

The OECD has approved several validated test guidelines that enable classification and assessment of skin sensitisation in combination with other defined approaches and information, without the use of animals. These methods each address a specific biological step in the development of skin sensitisation key events. Additionally, the Skin Sensitisation Risk Assessment – Integrated Chemical Environment (SARA-ICE) defined approach which is a predictive tool to estimate human relevant skin sensitisation potency, has been developed. When used together with other relevant information, these methods can be employed to determine both whether a substance is a skin sensitiser and how potent its effect may be for categorisation purposes.

These tests include:
- A protein binding assay called the direct peptide reactivity assay (OECD TG 442C),
- A keratinocyte assay (OECD TG 442D),
- A series of tests that identify dendritic cell activation (OECD TG 442E).
- SARA-ICE defined approach (OECD TG 497).

Animal tests are only used to satisfy regulatory testing requirements if these alternative methods do not provide enough data for decisions on the risk of skin sensitisation to be made confidently.

Target: By the end of 2026 we will aim to apply only validated alternative methods to satisfy UK regulatory requirements for skin sensitisation testing.

7. Replacing the use of animals in botulinum toxin batch potency testing

Batch testing of biological products uses large numbers of animals in assays that have the potential to cause severe suffering. In Europe, it accounts for the highest number of animals undergoing severe procedures across all research and testing.

Botulinum toxin, which includes eight different serotypes, is one of the most poisonous biological substances known. It is a potent neurotoxin produced by the bacterium *Clostridium botulinum* that blocks neural transmission causing muscle paralysis. At low doses it is clinically effective in many medical conditions including muscle spasticity, strabismus, hyperactive urinary bladder, excessive sweating, and migraine. Medicinal

products containing botulinum toxin may be prescribed for aesthetic applications including correction of lines, creases and wrinkling all over the face, chin, neck and chest.

Due to the high risk of batch-to-batch variability and the highly toxic nature of the product, all batches of botulinum toxin require potency testing for quality control. This is traditionally carried out in groups of up to 100 mice per test to determine the lethal dose that causes death (by asphyxiation) in 50% of the test population (LD50) over a three-to-four-day period. Despite improvements where humane endpoints are applied to alleviate animal suffering and prevent death as an endpoint, animals are expected to die because of these procedures. Several manufacturers of botulinum toxin have developed, or are developing, *in vitro* cell-based assays to replace the animal test, but issues with proprietary components mean that the full methodological details of these have not been shared or published. Additional non-animal methods are being developed by academic researchers.

The UK MHRA now accepts a non-animal alternative method for the testing of the most common and specific strengths of Type A botulinum toxin drug substances (the 500U BAS and 300U BAS drug substances), and since 2024 no longer licences the use of LD50 testing for third countries. The EU is also aligned with these testing requirements. However, *in vivo* testing remains permissible in certain cases, for example when it is needed for specific diagnostic assessment needs for clinical patients.

Target: By the end of 2027 we will aim to apply only validated alternative methods in the pharmacopoeial potency testing of botulinum toxin. Animal potency testing for botulinum toxin will be permitted only in the rare occasions where animal, human or food safety incidents require potency determination that cannot be conducted using the validated alternative methods.

8. Replacing animals in the development and quality control testing of veterinary medicines and vaccines

The UK's Veterinary Medicines Directorate (VMD) assesses applications submitted by the veterinary pharmaceutical industry in line with national and international regulations and guidance, to ensure safe and effective veterinary medicines of good quality are marketed. These requirements may necessitate animal testing either during the development and authorisation of new veterinary medicines or, in the case of some vaccines, for product quality control (QC) testing, to ensure the continued quality, safety and efficacy of each batch.

The requirement for the Target Animal Batch Safety Test (TABST) which was previously conducted on batches of veterinary vaccines was removed from the European Pharmacopoeia in 2013 and is no longer conducted on vaccines marketed in the UK or EU. Over the last decade several *in vitro* QC tests have been introduced as alternatives to *in vivo* testing, and the VMD strongly encourages manufacturers of veterinary medicines to use these tests where possible. Where it is mandated that an *in vivo* test is no longer needed, the VMD ensures that such testing is not conducted. *In vitro* alternative approaches for batch safety testing are already available for some vaccines, such as Leptospira and Erysipelas. However, animal use for certain vaccines may still be required to confirm safety.

Target: Following international competent authority acceptance of an alternative quality control (QC) test, we will aim to replace the use of animals in the UK for veterinary vaccine testing as soon as is feasible where these tests can be validated and implemented for the relevant veterinary vaccine.

Basket 2 – Tests that require further development in the medium term

This basket describes animal testing or models for which alternative methods exist but have not been validated or demonstrated to be sufficiently robust for widespread adoption to replace the current *in vivo* approach. Further research and development focused on demonstrating alternative methods are fit for purpose, together with cross-sector and cross-discipline collaboration, will be required in the medium term to enable the phase in of these approaches.

1. Replacing the forced swim test

The forced swim test (FST) is commonly used to assess the behavioural effects of antidepressants by placing a rat or mouse in a tank of water from which it cannot escape and where the water is deep enough that the animals cannot touch the bottom. The time the animal spends swimming or immobile is measured with increased swimming seen as an antidepressant effect. All approved antidepressants increase swimming behaviour in the FST.

The test has limited scientific validity, particularly its translational relevance to human mental health disorders. Animal behaviour in the FST also lacks information on treatment latency and varies across strains and protocols. Therefore, we would expect the Home Office Regulator's default position to be that the FST does not pass the harm-benefit test required under ASPA.

In response to a 2023 ASC report, the Home Office in 2024 committed to restricting licensing of the FST to only those instances when it is essential to the research question, no alternative method exists, the expected scientific or medical benefit is substantial and well-evidenced, and the study design includes robust measures to minimise animal suffering. While no accepted non-animal methods currently exist, research is ongoing into alternatives such as larval zebrafish, fruit fly models, and AI-based screening. Efforts are also underway to refine animal-based approaches, including the use of ultrasonic vocalisations, cognitive bias tests, and long-term behavioural monitoring in home cage settings.

We will continue to assess any new applications to use the FST as new alternatives are developed, against ASC recommendations which we have accepted. The current three active licences which authorise the use of the FST will conclude by 2028.

Target: We will no longer grant licences for the FST as a model of depression. In cases of screening for antidepressant efficacy and studying the neurobiology of stress, we will aim to support the validation of alternatives to FST by the end of this parliament to replace the use of the FST.

2. Replacing the fish acute toxicity test

Fish acute toxicity studies (as described in OECD TG 203) are the most widely conducted ecotoxicology tests, intentionally inducing mortality (which involves severe suffering) in test animals, with many thousands of fish used for regulatory purposes worldwide each year. The test aims to determine the concentration of a substance that causes death in 50% of the test animals (Lethal Concentration, LC50) during a 96h exposure. Fish acute toxicity tests are currently required to meet global regulations across many chemical sectors before products can be authorised for use, including agrochemicals, biocides and industrial chemicals.

Considerable evidence to support the adoption of methods that avoid the use of a fish acute toxicity test already exist. These include computational quantitative structure-activity relationship models (QSAR), *in vitro* cytotoxicity assays and the fish embryo toxicity test which uses embryonic stages of fish, prior to free-feeding which are therefore not protected under ASPA. Relevant validated OECD test guidelines include the Fish Cell Line Acute Toxicity – The RTgill-W1 cell line assay (OECD TG 249) and the fish embryo toxicity test (OECD TG 236). Data generated using a combination of these tests (and other approaches) can provide the weight of evidence needed and avoid the use of an *in vivo* fish test of high severity.

The UK is supporting work within the OECD Test Guidelines Programme with expert review and input, to assess the utility and validity of these alternative assays and their integration to replace fish testing against a broad range of endpoints and chemicals, that aims to be completed by 2027. This includes ongoing work at the OECD on an Integrated Approach to Testing and Assessment (IATA) for acute fish toxicity testing. Further, the European Commission is proposing that as part of the planned EU REACH revision, validated alternative tests – OECD TG 249 or OECD TG 236 – will be introduced to address acute toxicity without testing on fish for substances registered under REACH. Continuing dialogue with scientists, CROs, industry, and UK and international regulators will be essential in facilitating this and driving widespread implementation.

Target: We will aim to replace fish acute toxicity tests for chemicals registered under UK REACH with alternative methods by the end of 2028, and reduce such tests for pesticides and agrochemicals in line with international acceptance.

3. Reducing the use of animals in pharmacokinetic studies

Pharmacokinetic (PK) studies investigate how a drug is absorbed, distributed, metabolised, and eliminated by the body over time. They are carried out in most laboratory species to understand how a drug interacts with the human body, helping to determine safe and effective dosing regimens. Advances in PK prediction tools (e.g. based on AI and molecular structure) can be a viable alternative to many animal studies, however currently it is not possible to fully predict PK without *in vivo* data. Pharmacokinetic modelling

improvements may lead to fewer experiments *in vivo*, especially in the screening and candidate selection phase where many potential new drugs currently require comparative *in vivo* testing. Applying alternative methods earlier for PK assessments will mean only the final candidate will have to undergo *in vivo* PK testing in the future.

There are currently no alternative methods which fully predict *in vivo* pharmacokinetics. Greater access to (and generation of) more PK data across different compounds will accelerate and improve the predictivity of computational and AI models, and together with *in vitro* human tissue cultures, organoids or organ on a chip models could be integrated as part of an alternative combinatorial method. These require further development in parallel, especially for longer term exposure studies where maintaining cell functionality remains a challenge. To a large extent, kinetic data can be generated from other studies, e.g. general toxicity studies: the focus is to eliminate dedicated kinetic studies where the only objective of the animal study is to generate kinetic data.

Target: We will aim to use validated alternative methods to reduce the use of dogs and non-human primates in dedicated PK studies for human medicines by at least 35% by 2030.

4. Reducing animal use in cardiovascular safety studies

Cardiovascular studies are routinely conducted in animals, typically dogs and non-human primates, to monitor changes in heart rate, blood pressure, and electrical activity (e.g. ECG) after drug administration. These studies help detect risks such as arrhythmias or hypertension before drugs progress to human trials.

There are several indicative models to identify cardiac arrhythmia, including the validated hERG ion channel assay, which is included as a standard *in vitro* screening assay prior to regulatory *in vivo* studies. Regulatory guidance also supports newer approaches like the Comprehensive *in vitro* Proarrhythmia Assay (CiPA) initiative that employs a combination of *in vitro* assays, *in silico* modelling, and human stem cell-derived cardiomyocytes to predict the proarrhythmic potential of new drugs, but these are yet to be fully validated. Non-animal approaches combining human-based *in vitro* assays, including organoid or organ on a chip models, together with *in silico* assays capable of replicating the human cardiovascular system are a focus of many researchers globally.

We will work with regulators and the pharmaceutical industry to validate available non-animal methods for cardiovascular safety studies and accelerate their wider uptake. While this is being pursued we will encourage alternative testing strategies to reduce animal use, for example, combining cardiovascular studies into general toxicity studies.

Target: We will aim to use validated alternative methods to reduce the use of non-human primates and dogs in dedicated cardiovascular safety studies by at least 50% by 2030.

5. Phasing in the use of non-animal derived antibodies and affinity reagents

Antibodies are proteins with high specificity for their unique target and have been used as crucial tools for diagnostics, therapeutics, regulatory procedures, and research to

investigate molecular and cellular pathways. Antibodies are generated by repeated administration in an animal of an antigen to stimulate the production of antibodies which are then harvested by blood sampling. Large numbers of animals (including rodents, rabbits, goats, sheep and chickens) are used in antibody development and their utility is subject to debate due to issues of specificity and reproducibility. This is especially true for polyclonal-type antibodies (pAbs) which have significant batch to batch variation and often uncharacterised cross reactivities.

Several alternative technologies to traditionally derived antibodies exist, which do not use animals in their production, and which offer unlimited supplies of reagent with limited batch to batch variation. This includes recombinant antibodies (developed using phage display technology), affimers, aptamers and multiclonal antibodies which have all the advantages of pAbs and none of the drawbacks. Adoption of these non-animal alternatives has been limited, within the academic research community, by lack of awareness and education in their utility, commercial availability, and drivers to encourage their use.

In 2021, the ASC made several recommendations with respect to project licence applications proposing the use of animals for pAb production. This included the need to more thoroughly consider whether non-animal alternatives are valid and appropriate before approving future applications.

Target: We will aim to replace the use of animal-derived pAbs by 2030.

Basket 3 – No suitable alternative methods currently exist

This basket describes animal testing or models that focus on more complex endpoints for which no viable alternative methods currently exist, and their development and/or adoption are longer term aims.

1. Reducing the use of fish in assessing endocrine disruption

Fish endocrine disruptor assessment tests evaluate the effects of chemicals on the hormonal systems of aquatic vertebrates, helping to identify substances that may interfere with growth, reproduction, and development. These tests are critical for environmental protection and are increasingly considered within regulatory frameworks to ensure environmental and public health safety. Standardised assays, such as the Fish Short-Term Reproduction Assay (FSTRA, TG229) and Fish Sexual Development Test (FSDT, TG234), involve exposing fish to test substances and measuring endpoints like vitellogenin levels (a protein produced by the liver of female fish and is involved in egg yolk formation), secondary sexual characteristics, gonadal development, and sex ratios.

These tests are resource-intensive and use large numbers of animals. Opportunities for replacement include developing *in vitro* and embryo assays, computational models (e.g. QSARs), and adverse outcome pathways that link molecular-level effects to population-level impacts. To accelerate adoption, validation of these methods is crucial, alongside increased regulatory acceptance and international harmonisation. The UK is supporting the integration of cell-based and computational approaches in safety assessments, whilst moving away from protected animal testing via active participating in validation work at OECD but also via domestic and Horizon funded R&D programs.

Cross-sector collaboration among scientists, regulators, and industry will further drive innovation and build confidence in alternatives, enabling a transition to more humane, efficient, and cost-effective testing strategies.

Target: By the end of 2035 we will aim to include validated alternative methods in UK regulatory guidance to reduce the use of fish endocrine disruption tests.

Next Steps

Implementing the commitments in this plan will place the UK at the forefront of efforts to phase out the use of animals in science. This is the start, and we want to move fast where we can. It will likely take many years of scientific and technological effort to fully replace animals, but a lot can be done now. As we move into implementation, we will work closely with experts from across the many fields involved in this area, including regulators, academics, industry and civil society organisations, to ensure that this strategy remains up to date and focused on the key issues.

Abbreviations

Abbreviation	Full form
3Rs	The Replacement, Reduction and Refinement of animals used in research
ABPI	Association of the British Pharmaceutical Industry
AI	Artificial intelligence
ASC	Animals in Science Committee
ASPA	Animals (Scientific Procedures) Act 1986
ASRU	Animals in Science Regulatory Unit
AWERB	Animal Welfare Ethical Review Body
Cefas	Centre for Environment, Fisheries and Aquaculture Science
CEiRSI	Centre of Excellence on *In silico* Regulatory Science and Innovation
CRO	Contract research organisation
Defra	Department for Environment, Food & Rural Affairs
DHSC	Department for Health and Social Care
DSIT	Department for Science, Innovation and Technology
EA	Environment Agency
EMA	European Medicines Agency
EPA	United States Environmental Protection Agency
EPAA	European Partnership for Alternative Approaches to Animal Testing
FDA	United States Food and Drug Administration
FSA	Food Standards Agency
HSE	Health and Safety Executive
HTS	High Throughput Screening
ICATM	International Cooperation on Alternative Test Methods
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IHI	Innovative Health Initiative
ISO	International Organisation for Standardization
iPSC	Induced pluripotent stem cells
MHRA	Medicines and Healthcare products Regulatory Agency
NACRARS	New Approaches to Chemical Risk Assessment in the Regulatory Space

Abbreviation	Full form
NC3Rs	National Centre for the Replacement, Refinement and Reduction of Animals in Research
NDL	National Data Library
NICEATM	The NTP (National Toxicology Program) Interagency Center for the Evaluation of Alternative Toxicological Methods
OECD	Organisation for Economic Co-operation and Development
PARC	Partnership for the Assessment of Risks from Chemicals
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
UKCVAM	UK Centre for the Validation of Alternative Methods
UKHSA	UK Health Security Agency
UKRI	UK Research and Innovation
VICH	Veterinary International Conference on Harmonization
VMD	Veterinary Medicines Directorate
WHO	World Health Organisation

Glossary

Word, Phrase or Abbreviation	Description
3Rs	The principles of Replacement, Reduction and Refinement of animals used in research. They aim to reduce reliance on the use of animals and minimise pain, suffering and distress in those animals still required. (a) the principle of replacement is the principle that, wherever possible, a scientifically satisfactory method or testing strategy not entailing the use of protected animals must be used instead of a regulated procedure; (b) the principle of reduction is the principle that whenever a programme of work involving the use of protected animals is carried out the number of protected animals used must be reduced to a minimum without compromising the objectives of the programme; (c) the principle of refinement is the principle that the breeding, accommodation and care of protected animals and the methods used in regulated procedures applied to such animals must be refined so as to eliminate or reduce to the minimum any possible pain, suffering, distress or lasting harm to those animals
Alternative methods	A broad range of tools and technologies, including cell culture-based approaches and computational modelling, that can reduce or replace animal use across the whole of the bioscience landscape
Animals (Scientific Procedures) Act 1986 (ASPA)	Regulates the use of protected animals in any experimental or other scientific procedure which may cause pain, suffering, distress or lasting harm to the animal. Protected animals under the Act are any living vertebrae other than man and any living cephalopod. Embryonic and fetal forms of mammals, birds and reptiles are protected animals once they have reached the last third of their gestation or incubation period. Larval forms of fish and amphibians are protected animals once they are capable of feeding independently. Cephalopods are protected animals from the point when they hatch.
Animals in Science Committee (ASC)	An independent advisory body that provides impartial advice to the Home Office and other related bodies on issues concerning the use of animals in scientific procedures. It operates under the Animals (Scientific Procedures) Act 1986 and its functions.

Word, Phrase or Abbreviation	Description
Animals in Science Regulation Unit (ASRU)	A UK government body within the Home Office responsible for ensuring compliance with the Animals (Scientific Procedures) Act 1986 (ASPA). Its primary purpose is to protect animals used in scientific research by overseeing their use and ensuring adherence to regulations.
Animal Welfare and Ethical Review Body (AWERB)	An essential component of improving science and animal welfare. Under the ASPA, all establishments using, breeding or supplying animals for scientific procedures must have one. AWERBs are tasked with ensuring that all use of animals in an establishment is carefully considered and justified; that proper account is taken of all possibilities for the 3Rs; and that high standards of accommodation and care are achieved.
Biocompatibility	A material's ability to interact appropriately with living tissues without causing adverse reactions like inflammation or rejection
Bioengineering	The application of engineering principles and techniques to solve problems and improve practices in the fields of biology and medicine. It involves using engineering design and analysis to address issues in living systems, develop new technologies, and create innovative solutions for health and other biological applications.
Bioprinted construct	The use of bioprinting approaches, where cells are mixed with bioinks and biomaterials, to create natural tissue-like three dimensional structures.
Cytotoxicity	A substance or process that can damage cells or cause them to die
Discovery research	A type of research focused on exploring a new or little-known area of inquiry to expand knowledge and understanding of underlying phenomena without a specific, practical application in mind. It may also be termed basic or fundamental research.
Efficacy	The ability of an intervention (for example, a drug or surgery) to produce the desired beneficial effect.
Genotoxicity	The ability of a substance to damage the genetic material (DNA) within cells, potentially leading to mutations and other adverse effects like cancer, birth defects, or developmental problems. It is a measure of how toxic a substance is to DNA.

Word, Phrase or Abbreviation	Description
Induced pluripotent stem cells (iPSC)	Adult cells, typically skin or blood cells, that have been reprogrammed in a lab to resemble embryonic stem cells. This reprogramming allows iPSCs to differentiate into any cell type in the body, making them valuable tools for research and potential therapeutic applications
In silico	Experiments performed by computing platforms or custom hardware, encompassing mathematical modelling and simulation, machine learning, artificial intelligence and other computational techniques.
In vitro	Experiments performed on cells outside of the body, including various types of cell, organoid, and tissue culture techniques.
Next generation sequencing	A high-throughput technology that allows for the rapid and efficient sequencing of DNA or RNA, enabling researchers to study genetic variation and other biological processes
New approach methodologies	Non-animal methods used for assessing chemical or drug toxicity and safety
Non-animal methods	Tools and techniques used to replace the use of animals (defined as those protected under the Animals (Scientific Procedures) Act 1986 (ASPA)) where they would traditionally have been used, irrespective of purpose
Omics research	A field that investigates all the different types of molecules within a cell, tissue, or organism. It uses technologies to study the complete set of DNA (genomics), RNA (transcriptomics), proteins (proteomics), metabolites (metabolomics), and other molecules to understand the relationships and roles of these molecules in a living system
Organoid	A self-organised 3D tissue that is typically derived from stem cells (pluripotent, fetal or adult), and which mimics the key functional, structural and biological complexity of an organ.
Organ-on-a-chip	A microfluidic device designed to simulate the structure and function of a human organ in a laboratory setting. These chips contain microchannels that replicate the internal structures of an organ, like blood vessels, and are populated with living cells that behave similarly to the cells in the actual organ
Pharmacokinetics	Explores the effect of the body on a compound (drug or chemical for instance) resulting in the absorption, distribution, metabolism and elimination properties of the compound.
Pharmacodynamics	Explores the effect that a compound (drug or chemical for instance) has on the body.

Word, Phrase or Abbreviation	Description
Qualification	A process by which a non-animal method is demonstrated to be fit-for-purpose; and have sufficient reliability and rigor in a specific context of use to give confidence that decisions made based on data generated in these methods are robust. Qualification may also set expected criteria to be used in the subsequent validation.
REACH regulation	The main EU law designed to protect human health and the environment from the risks posed by chemicals. It aims to ensure a high level of protection by requiring businesses to assess and manage the risks associated with chemicals, and by promoting the use of safer alternatives. The UK established its own version of REACH (UK REACH) following the UK's withdrawal from the EU
Regulated procedure	Any procedure applied to a protected animal for a scientific or educational purpose that may cause the animal pain, suffering, distress, or lasting harm, equivalent to or greater than that caused by inserting a hypodermic needle in accordance with good veterinary practice
Regulatory research	Focuses on developing the scientific knowledge, tools, and approaches needed to assess the safety, efficacy, quality, and performance of regulated products. It underpins regulatory decision-making, ensuring the safety and effectiveness of products for patients and consumers.
Spheroids	Simple, spherical cell aggregates, often consisting of a single cell type, formed by cells aggregating in suspension or on non-adherent surfaces.
Stem cell approaches	Using the unique properties of stem cells – their ability to self-renew and differentiate – to study and understand human biology and develop new therapies. These approaches include using stem cells to model diseases, test drugs, and potentially regenerate damaged tissues.
Tissue microenvironment	The cells, molecules, and structures that surround and support other cells and tissues within an organ or tissue. It's a dynamic and complex network that plays a crucial role in maintaining tissue homeostasis and influencing various biological processes, including development, repair, and disease.
Translational research	The process of translating scientific discoveries, often from discovery research, into real-world applications that improve human, animal and environmental health

Word, Phrase or Abbreviation	Description
Test guidelines	Sets of internationally recognised standards for nonclinical safety testing, primarily for chemicals and pharmaceuticals. They are developed to ensure the safety and efficacy of substances before they are used or marketed.
Toxicity	The extent to which something is poisonous or harmful
Validation	A process by which a non-animal method is demonstrated to consistently produce reliable results meeting pre-determined quality standards and acceptance criteria in a specific context of use. Validation of a test method is required for data generated in them to be accepted for regulatory decision making.

Annex – Strategy Commitments

Number	Theme	Action	SRO	Date
1	Discovery Research	Create a preclinical translational models hub	Executive Chair, MRC	By end of 2026
2	Discovery Research	Increase investment in alternative methods.	UKRI	Start in 2026 funding cycle
3	Discovery Research	Enable funders to ensure thorough scrutiny of animal research in funding decisions	UKRI	Start in 2026 funding cycle
4	Discovery Research	Provide foundational training for early career researchers in alternative methods	Chief Executive, NC3Rs	Start in 2026 funding cycle
5	Discovery Research	Publish areas of research interest for alternative methods	UKRI	Initiate in H1 2026
6	Discovery Research	Strengthen the commitment of journal editors to publishing research using alternative methods	Chief Executive, NC3Rs	Initiate at start of 2027
7	Discovery Research	Increase the visibility of available alternative methods to facilitate their uptake	Chief Executive, NC3Rs	By end of 2026
8	Discovery Research	Accelerate uptake in alternative methods through reform of animals in science regulation	Head of ASRU, Home Office	Complete by end of 2026
9	Validation and regulatory uptake	Establish a UK Centre for the Validation of Alternative Methods (UKCVAM)	Director, Office for Life Sciences	By end of 2026
10	Validation and regulatory uptake	Publish regulatory agency accepted alternative methods and priorities for future development and validation	Chief Executive, NC3Rs	By end of 2026
11	Validation and regulatory uptake	Expand challenge-led innovation for alternative methods	UKRI	Start in first 2026 funding cycle

Number	Theme	Action	SRO	Date
12	Validation and regulatory uptake	Support training in alternative method development, qualification and validation	Chief Executive, NC3Rs	Have infrastructure and program in place by start of 2027
13	Validation and regulatory uptake	Supporting the upskilling of regulatory assessors	Director, Office for Life Sciences	Have program in place by end of 2026
14	Validation and regulatory uptake	Develop mechanisms to enable regulators to provide pre-submission feedback	Director, Office for Life Sciences	Initiate in 2026
15	Validation and regulatory uptake	We will quantify annually the inclusion of second species testing in clinical trial applications	Chief Executive, NC3Rs	First publish by mid-2026
16	Data	Increase investment in data-driven biology	UKRI	Initiate in 2026 funding cycle tied into LSSP
17	Data	Establish data sharing frameworks to support the equitable access to public and private data sources	Director, Office for Life Sciences	Complete in 2026
18	Data	Enhance data curation and quality control and develop regulatory frameworks for data use	Director, Office for Life Sciences	Complete in 2026
19	International	Establish the UK as a global leader in the regulation and science of alternative methods	Director, Office for Life Sciences	Complete by end of 2026
20	International	Launch specific projects to secure international acceptance	UKCVAM	Align with first funding cycle by end of 2026 when UKCVAM established

Number	Theme	Action	SRO	Date
21	International	Host an international meeting of regulators in the UK on the validation and acceptance of alternative models	Director, Office for Life Sciences	Establish in H1 2027
22	Effective Governance	Provide Ministerial leadership on alternative methods	Director, Office for Life Sciences	Initiate in H1 2026
23	Effective Governance	Formally involve DSIT in the direct commissioning and receipt of advice from the ASC	Director, Office for Life Sciences	Initiate in H1 2026
24	Effective Governance	Enable better advice on alternative methods	Head of ASRU, Home Office	Initiate in H1 2026
25	Effective Governance	Restart the survey on public attitudes to animal research	Director, Office for Life Sciences	Initiate in H1 2026
26	Effective Governance	Establish KPIs with which to assess the delivery of this strategy	Director, Office for Life Sciences	Initiate in H1 2026

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978-1-5286-5871-3