Replacing Animal Research

Reducing animal testing in the health sector through strategic investment:

Prepared for Stewart Investors

Institute for Sustainable Futures

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About the authors

ISF is an independent research institute within the University of Technology Sydney. We conduct transdisciplinary, project-based research in line with our vision of creating positive change towards sustainable futures.

The University of Adelaide has research strengths at the intersection of animal research, public understanding of science, and ethical consumption as reflected in this report.

Replacing Animal Research (formerly the Fund for the Replacement of Animals in Medical Experiments or FRAME) is a charity based in the United Kingdom which develops and promotes alternatives to animal testing by funding research, education, and policy work.

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Disclaimer

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Executive summary

Introduction: the issue

Animal testing remains prevalent in many companies operating within the pharmaceutical, healthcare, and wellness sectors. This is in spite of recent regulatory changes, notably in the EU, to advance the use of non-animal methods, and consequentially reduce animal numbers. This report was commissioned by Stewart Investors to aid in their understanding of methods being used in the pharmaceutical, healthcare, and wellness sectors to reduce animal use, as well as barriers to this. A key aim was to identify best practices associated with transitioning to non-animal approaches and creating visibility around this. This information has been incorporated into a guide which can be used when making decisions around this topic prior to investing.

Stewart Investors employed a joint team from the Institute for Sustainable Futures at UTS and The University of Adelaide together with support from Replacing Animal Research (formerly the Fund for the Replacement of Animals in Medical Experiments or FRAME) to undertake research on current policies and practices relating to animal testing in a sample of companies selected by them. This report presents the key findings and insights from that research project without identifying companies included in the study. Stewart Investors was provided with a confidential report that provided detailed findings for each company. The companion Investor Guide offers guidance for investors seeking to engage on this issue.

Barriers to implementing alternatives to animal testing

Despite widespread awareness and endorsement of the 3Rs–replacement, reduction, and refinement–within legislation and company policies, there is a focus on the latter two ‘R’s’. Barriers to implementing alternatives include:

- Regulatory requirements, predominantly around compound/drug registration which are especially significant in the pharmaceutical sector.
- Lack of training and expertise in the validity, and use of alternatives in the context of biomedical and other forms of testing.
- Institutional patterns that reinforce the use of animals. These include that standardised strains are commercially available and well-accepted as models, and that standards of effectiveness may be unclear when considering non-animal methods. As an example, researchers may erroneously believe that animal and non-animal models need to show the same outcomes, through being contrasted directly.

Research methodology

A questionnaire was derived to assess company practices related to animal experimentation, and implementation of alternatives to animal testing. The draft survey was refined based on expert feedback and piloted on three companies prior to use. The questionnaire was then used to assess a sample of 21 companies selected by Stewart Investors. The research team applied the questionnaire to publicly available company data, obtained through perusal of websites. Following this, the questionnaire was refined to only include the highest priority questions. The refined question set, and a copy of our findings, were then sent out to the investor relations teams of the companies, with a request for completion. Most companies failed to respond to the request or provided very basic responses. A qualitative analysis of each of the company’s current practices, and responses are provided in this report.

Key findings

We found a lack of company transparency around research animal use within publicly available information. The majority of companies failed to respond to our direct request for information. From the limited responses received there also appears to be limited engagement with other companies in the sector, or with regulators to encourage greater use of non-animal methods. Most companies failed to provide information on the numbers of animals used, and trend in use over recent years. Many companies appear to outsource some or all of their animal testing to external Contract Research Organisations (CROs) which makes assessment of

their practices extremely complex given different regulatory requirements in each jurisdiction. Few companies provided details about their participation in audit or accreditation schemes in relation to animal testing, or details about their plans for developing or using non-animal approaches. No companies provided time-bound targets for implementing non-animal approaches or reducing use of experimental animals, or about outreach programs to inform the public about their commitments in relation to reducing animal testing. Several companies noted that the topic of animal testing was evaluated as part of their materiality assessment when reporting on sustainability. In these cases the topic was deemed to be immaterial and not of particular business risk to them. This points to a general lack of pressure or incentives for companies to either disclose or actively engage with the issue.

Given the low baselines in company disclosure around this topic and a relative lack of appetite for engaging further around this issue, it will be important to prioritise achievable short- and medium-term goals, such as encouraging greater transparency and openness in line with global agendas. This will support building of public trust in these companies, and the sector. It will also allow for increased understanding on the barriers to adopting alternatives.

Key engagement points

In their company interactions, investors should focus on transparency as a way that companies can showcase their efforts into promote the 3Rs. Key issues relate to disclosure and policies in relation to animal use by subsidiaries and contractors. Investors can also encourage the setting of timebound targets associated with transitions to non-animal testing, where permitted by regulation. Investors can promote company change by emphasising that animal testing and transitioning to non-animal methods are important issues to them. Highlighting that this issue is one that can materially affect their investment decisions, and the reputation of the companies in question, will assist in accelerating progress towards non-animal research.Investors can also support advocacy by encouraging companies to engage with the regulatory sector around non-animal methods, and by upskilling staff around the availability and use of non-animal methods.

Contents

Introduction

Stewart Investors commissioned this research to allow them to increase their understanding of the latest alternatives to animal-based testing, and to determine the extent of non-animal model usage within the pharmaceutical, healthcare, and wellness sectors. The research explored any company-stated barriers to adoption of alternative methods, and examples of best practices in making this transition. A joint team from the Institute for Sustainable Futures at UTS and The University of Adelaide, together with support from Replacing Animal Research (formerly the Fund for the Replacement of Animals in Medical Experiments or FRAME), was employed for this work. The research focussed on a sample of geographically diverse companies selected by Stewart Investors. This report presents key findings and insights from this research but does not identify the companies included in the study. Stewart Investors was provided with a confidential report that provided detailed findings for each company.The project team has prepared a separate companion Investor Guide to support investor engagement in this domain. This guide provides a framework to support advocacy, and encourage transitions to non-animal methods, as well as promoting company transparency around animal research.

Global trends in animal testing in the healthcare sector

The current state of animal testing practices

The term 'animal testing' generally refers to a range of procedures performed on living animals for the purpose of: doing research into fundamentals of biology and understanding of disease; assessing the effectiveness of new medicinal products; and identifying adverse effects, including toxicity for humans and/or environmental safety of consumer and industrial products (such as cosmetics, household cleaners, food additives, pharmaceuticals, and industrial and agrichemicals).[1] Animal testing is conducted in a range of settings including universities, research institutes, pharmaceutical companies, and commercial facilities that provide services to industry, and tends to be used when human experimentation would be unfeasible, difficult or extremely expensive to perform in a standardised manner, or unethical.

A significant proportion of animal-based testing in the pharmaceutical and healthcare sectors is used to determine the efficacy and safety of new drugs and medical devices before they can go into phased human clinical trials testing and be approved for human use. This market approval is regulated via a variety of agencies, which operate across the relevant jurisdictions e.g. FDA, European Medicines Agency. It is commonly cited that these regulatory requirements are a significant barrier to further reduction and replacement of animal use. Tests on animals are usually done for three main purposes:

1) to test the efficacy of the drug or device in treating a specific condition, or enabling a specific function;

2) testing the pharmacokinetics and pharmacodynamics of a drug to investigate how it is absorbed, distributed, metabolised and excreted (ADME testing) by the body;

3) testing the safety of the drug or product to evaluate any potential adverse effects and to determine the dose at which a substance is toxic.

Whilst there have been considerable advances in replacing animals for 2, and 3) relatively less attention and success has been achieved in promoting animal replacements in efficacy testing.

Although this report focuses on the health sector, it is important to note that bans have been put in place on animal testing (and/or trade of products tested on animals) in the cosmetics sector in recent years in many countries within the European Union, Norway, Switzerland, Israel, South Korea, India, Australia, and New Zealand, as well as in certain states within the United States. [2] These bans reflect changing public opinions

[1] We do not explore the use of non-human organisms to make biologically derived products (e.g., use of animal tissue in human implant products) as these applications were deemed to be out of scope for the current project.
[2] The U.S. Food and Drug Administration (FDA) defines cosmetics as "articles intended to be applied to the human body for cleansing, beautifying, promoting attractiveness or altering the appearance without affecting the body's structure or functions." Examples include perfume, moisturizer, nail polish, makeup (such as mascara and lipstick), and hair products (such as hairspray and conditioner), as well as any ingredient used in a cosmetic. Cosmetic products can also be classified as drugs when a medical claim is made (e.g., toothpastes with cavity protection or lotions that contain sunscreen). For

about animal testing but also the relative maturity of this type of industry since many cosmetic products have been extensively tested and are now considered to be safe. In addition, even where continued safety testing is required in the cosmetics sector, there are many well-recognised alternatives to intact, live animal use such as using cell lines or cultures.

In the biomedical or health sector, research using non-human animals is often credited with considerable success. The development of laparoscopic surgery techniques, a highly successful polio vaccine, and antibiotic developments are common stories showcasing the benefits of animal research. However, success stories abound across medical research pursuits, spanning contributions to basic knowledge, development of effective therapeutics and surgical interventions, as well as vaccinology. As a result, advocates regard animal testing as the cornerstone of modern, scientific medical research. Yet, a growing number of critics question the reliability and replicability of animal models, pointing to relatively high rates of failures of translation between non-human animals and humans. Other concerns relate to the suffering and other harms caused to experimental animals, and the challenges in reliably assessing welfare in sentient non-human animals. An often-vocal minority completely reject any use of non-human animals, based on animal rights arguments. They also assert that discussion of 'alternatives' be avoided since this assumes that current animal use practices are valid or ethical.

Animal welfare is a long-standing issue of concern for consumers including in the healthcare domain. Although data specifically on investment in relation to animal experimentation is not generally available, recent research by the Responsible Investment Association Australia (RIAA) notes that consumer concern about cruelty to animals has increased in the past two years. In 2024, RIAA found that 74% of Australians wish to avoid animal-related issues when investing, 66% cite animal cruelty as important to avoid in investment (making it the top-cited issue overall amongst human rights and environmental issues related to investment), and 54% want to avoid animal testing for non-medical purposes when they invest. Despite these findings, only 11% of Assets Under Management in Australia are screened in relation to animal testing.[3]

Most animal research is performed using rodents (mice and rats), fish, amphibians, and reptiles. Accurate data are difficult to source because countries collect information differently, if at all. Annual rates of vertebrate animal experimentation–with organisms ranging from zebrafish to non-human primates–were estimated to be 192 million as of 2015.[4] Per annum, 2.68 million procedures involving any kind of animals occurred in the United Kingdom (2023), and nearly 8.4 million animals were used in the European Union and Norway combined (2022). US figures are around 1 million (2021), relatively lower than in Europe since the figure excludes mice, rats, fish, and birds which are not captured in the research regulatory framework.

Whilst efforts to reduce animal use have been implemented in many institutions, and countries, these are widely thought to have been offset by continued increases in the use of mice due to the development of genetically modified strains to target specific disease conditions. Additionally, many countries have updated policy to require that both males and females are used in testing.[5] As a result, many countries report rising total animal numbers, but declines in the numbers of cats, dogs, non-human primates, rabbits, guinea pigs, and hamsters utilised. The rates of animal experimentation in regulatory testing and the pharmaceutical industry have shown the greatest decreases in recent years: 45% decline in use of animal for regulatory purposes in the European Union between 2015–22, and 31% decrease in commercial institutions in the United Kingdom in 2001–20. However, the overall small rates of decline (e.g., 4% total over the years 2015–22 in the European Union) indicate that animal testing is not likely to be eliminated given current trends.[6]

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more details, see https://www.fda.gov/regulatory-information/laws-enforced-fda/federal-food-drug-and-cosmetic-act-fdc-act.

[3] https://responsibleinvestment.org/wp-content/uploads/2024/03/From-Values-to-Riches-2024_RIAA.pdf

[4] Taylor, K., & Alvarez, L.R. (2019). An estimate of the number of animals used for scientific purposes worldwide in 2015. *Alternatives to Laboratory Animals* 47(5–6): 96–213. https://doi.org/10.1177/0261192919899853

[5] Ankeny, R.A., Whittaker, A.L., Ryan, M., Boer, J., Plebanski, M., Tuke, J., & Spencer, S.J. (2023). The power of effective study design in animal experimentation: Exploring the statistical and ethical implications of asking multiple questions of a data set. *Brain, Behavior, and Immunity* 112: 163–172. https://doi.org/10.1016/j.bbi.2023.06.012

[6] Taylor, K. (2024). Trends in the use of animals and non-animal methods over the last 20 years. *Alternatives to Laboratory Animals* 41(4): 503-24. https://doi.org/10.14573/altex.2410111

Broader contexts that shape animal testing practices

Animal research practices are significantly influenced by regulation in the jurisdictions in which they occur. The European Union and the United Kingdom are generally regarded as having the most stringent legislative requirements. Specific processes associated with approvals for animal testing differ according to geographic location, but generally involve review and oversight by some form of institutional ethics committee which may or may not have central (government) oversight.

Strict requirements around testing of products destined for patients or consumers date back to the late 1930s, with the U.S. Food and Drug Administration (FDA) driving practices, since the United States is the most significant market for many drugs. Notably the FDA has recently signalled that animal testing is no longer strictly required for registration, but has not accepted alternative evidence from many companies. This seeming dichotomy in actions is currently being played out in the courts. In a similar vein, the European Union has recently implemented regulations to eliminate use of animal testing in toxicology and other regulatory research, with the United States expected to soon follow suit.

As a relative success story, cosmetic testing on animals has been banned or is in phaseout in many jurisdictions including the European Union, United Kingdom, Norway, Australia, India, and Canada, but not the United States.

Voluntary pledges also shape animal testing practices. For instance many companies in the United Kingdom are signatories to the Concordat on Openness on Animal Research,[7] which has enhanced disclosure on animal testing, but has also been critiqued by some as being a form of 'humane washing.' Similar voluntary agreements exist in other countries including France, Switzerland, and Australia. Supporters argue that more transparency and openness will result in increased public trust and assist in legitimising animal research practices where they continue to be required. However, many companies, and individual researchers remain concerned that being more transparent will increase exposure to animal rights activism and create reputational damage. This is despite a significant decline in disruptive and destructive animal rights activism over recent years, alongside strengthened laws to deter perpetration of criminal activities associated with this.

A further consideration around companies operating in a global market is that it is common for them to have subsidiaries to expand their geographical market. This could allow animal research to be conducted at a different standard to that expected in the location where they are headquartered, and may be regarded as a 'loophole' of sorts. Many companies also outsource testing to external entities (Contract Research Organisations) which may operate in again in more favourable regulatory settings or deliver cost savings. Many of these may be in parts of Asia. In spite of this, companies still need to adhere to the standards established by the market in which they are looking to introduce their products. For example, the FDA for the US market. All of these factors make it difficult to fully track the numbers of animals utilised, the purposes for which they are used, and any one company's total portfolio of animal experimentation activities.

Alternatives to animal research in the health sector

The three Rs

The three Rs (3Rs) as initially described by WMS Russell and RL Burch in 1959[8] – replacement, reduction, and refinement–have become widely used as guiding principles for animal research. As a result, they are typically encoded in regulation across most of the world. 'Replacement' refers to the preferred use of methods that do not use animals yet still achieves the desired scientific aims with the same level of rigor and accuracy. 'Reduction' emphasises using fewer numbers of animals wherever possible while still obtaining comparable levels of information to that which would be possible using animals. 'Refinement' focuses on utilising methods that improve welfare, through minimising pain, suffering, or distress. Hence alternatives to animal testing have long been mooted, together with recognition of the need to improve animal welfare and scientific rigour especially where use of animals cannot be avoided. It is generally considered that replacement presents the greatest challenge to address.

[7] https://concordatopenness.org.uk/
[8] Russell, W.M.S. and Burch, R.L. (1959). *The Principles of Humane Experimental Technique.* London: Methuen.

Replacement techniques

Replacement techniques are sometimes grouped under the descriptor of 'new approach methodologies' or NAMs.[9] Such approaches can include:

1) *in silico* methods such as computer modelling, simulations, and mathematical calculations;

2) *in vitro* techniques using cells or cell lines, tissues, organoids, or organs on chips, imaging, biochemical analyses, genetics, and gene profiling; or

3) others such as the use of human research subjects, or reuse of existing data via meta-analysis or using AI to find patterns, or similar.

In some cases, alternative approaches are understood to include replacement of higher-level organisms and vertebrates with lower-level non-vertebrates, or the use of cells or other biomaterials from organisms, and hence still require some use of animals (so-called relative replacement). Thus, in this report, we use the terminology of 'non-animal' methods or models to distinguish such hybrid systems categorised as NAMs from those that do not involve testing on intact animals.

Toxicological and pharmacodynamic testing in the early-stage development of new drugs is often performed with *in vitro* models such as cell lines and recombinant DNA technologies rather than with intact live animals. With increasing recognition of the validity of use of non-animal methods, including in recent European Union regulations, it has been proposed that these types of methods may be useful more broadly for various types of experimentation in health care and related fields. Much toxicological testing typically used to determine adverse human reactions and tolerance to specific chemical substances has pivoted to use lower-level, non-vertebrate organisms or cell cultures. For instance, the Organisation for Economic Co-operation and Development (OECD) has recently approved *in vitro* assays for skin irritation and sensitization as well as basic toxicity at a genetic level. However, it is important to note that although there is increasing awareness of, and interest in non-animal approaches, there are limited numbers of established models for many of the later stages of research. Such approaches are particularly lacking for research where pharmaceutical or other types of activity must be assessed at an intact, organismal level with attention to its translation to humans including in pharmacological, therapeutic, or related studies and especially where determining efficacy in treating a condition is the main goal.

Barriers to development and adoption of alternatives

Despite increasing awareness of the importance of developing replacement methods, progress has been slow. For instance, recent research by NC3Rs on the World Health Organisation (WHO) guidelines for animal use in quality control and batch release testing in vaccines found that animals are still widely used with development and uptake of non-animal technologies being low. This is in spite of overall awareness of the 3Rs being high. Significant barriers exist at the level of the institutional ethics review process. Key ones relate to lack of training and knowledge of committee members around alternatives, which prevents a lack of meaningful questioning around their ability to be used. As has already been discussed, regulatory requirements present a significant barrier, especially for companies in the later testing phases. Other barriers include a general lack of training and expertise in using alternatives in the context of biomedical and other forms of testing, with many of these developments arising from disciplines outside of those where biomedical researchers are comfortable. Institutional patterns also tend to reinforce use of animals, particularly rodents, due to the widespread commercial availability of strains, and significant history of data to use for cross comparisons.

[9] Note: we define NAMs as "as any in vitro, in chemico or computational (in silico) method that when used alone, or in concert with others, enables improved chemical safety assessment through more protective and/or relevant models and as a result, contributes to the replacement of animals." From: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10964841/#:~:text=New%20approach%20methodologies%20(NAMs)%20can%20be%20defined%20as%20any%20in,to%20the%20replacement%20of%20animals.

Methodology

This section describes the research method and processes and summarises the Assessment Framework developed for this research project.

Overview

1. We developed a research questionnaire to assess company practices related to animal experimentation and implementation of alternatives to animal testing. The questionnaire comprised 37 questions, including 18 on the company's general engagement in and approach to animal testing, and 19 exploring specific practices related to alternatives to animal testing. This questionnaire was used to explore a sample of 21 companies selected by Stewart Investors as companies of interest to them. Stewart Investors previously undertook research using Sustainalytics data to identify companies that undertook or were likely to undertake animal research. Stewart Investors had also previously reviewed company websites around this topic and approached a sub-selection of companies directly for information. Stewart Investors provided their findings to us for incorporation into the current project. This Research received approval from the ISF Ethics Committee of UTS and was conducted in accordance with the provisions of the National Statement on Ethical Conduct in Human Research.
2. We undertook interviews with four experts in animal research, and alternatives. These experts were diverse in terms of their employment role (NGOs, researcher-related advocacy groups) and geographical location (United Kingdom, European Union, United States, and Australia/New Zealand). The experts provided background on the latest developments and dominant practices in these fields and discussed barriers to development and use of alternatives to animal testing. We also sought their feedback on the draft questionnaire and implemented this wherever possible. Information provided by these experts has been integrated throughout this report.
3. In order to answer our survey questions, we initially reviewed publicly available data accessible from the companies' websites. There was insufficient publicly available data to be able to complete in its entirety the questionnaire for *any* of the companies. This finding is significant as it underscores that investors are not likely to be able to source information using publicly available resources.
4. We then asked companies to provide further information and fill in gaps in their publicly available information using an abridged version of the questionnaire which focused on the highest priority questions. This second survey was pre-filled with information from the initial desktop research.
5. The companies were approached via an email to the investor relations team, with details having been provided by Stewart Investors. The companies were given at least 6 weeks to respond and reminder emails were sent. Most companies did not respond to the information request or provided very basic responses.
6. Based on the responses and information collected, a qualitative analysis of each company's current practices and approaches to alternatives to animal testing was compiled.

Assessment framework/questionnaire

The Assessment Framework that was constructed for this research used a standardised qualitative questionnaire (Appendix A). This aimed to track companies' practices associated with animal experimentation, and their development and use of non-animal approaches. A secondary aim was to assess their openness and transparency about these practices. The questions were devised based on the research team's expertise and experiences in this area together with feedback from experts as noted above. It asked for direct metrics such as numbers of animals used and rates of reduction, as well as less tangible measures of activities in this domain, for example collaborations with others in the sector, and engagement with regulators. The original questionnaire was structured to enable desktop data collection from publicly available information provided by the company. This survey covered the key issues that we hoped to see included in public disclosures. The abridged version reduced the number of questions, and hence the level of detail, to make it easier for companies to provide a subset of prioritised information and to maximise the response rate. The use of non-animal methods can be seen as a process of transition away from animal testing. Hence in developing the

questionnaire, the research team drew on elements of transition frameworks in other areas, notably climate change. The questionnaires were structured to explore how companies were approaching non-animal methodologies through consideration of:

- public commitments relating to use of animal testing and alternatives;
- disclosure of data on use of animals in the companies' operations, in-house or outsourced;
- targets to reduce animal testing;
- actions to support achievement of targets;
- investment in alternatives;
- reporting on progress;
- governance of use of animal testing and alternatives, including oversight and staff training;
- engagement in audit and quality processes relating to testing, alternatives, and animal welfare;
- understanding of risks associated with animal testing, and opportunities related to alternatives;
- disclosure of regulatory requirements;
- active engagement in promoting use of non-animal approaches and supporting transition beyond the company; and
- management of animal testing and alternatives in suppliers.

Data used in the assessment

Table 1 summarises the types of information used to assess each copmany in the study.

Table 1 Summary of data used in assessment

Company	Public data	Written responses
1	minimal	x
2	minimal	x
3	minimal	x
4	minimal	x
5	none	x
6	minimal	x
7	some	✔ minimal information provided
8	minimal	x
9	minimal	x
10	some	✔
11	none	x
12	some	✔
13	minimal	✔ minimal information provided
14	none	x
15	N/A	✔ stated that the company does not undertake animal testing
16	minimal	x
17	✔	✔
18	minimal	x
19	minimal	✔ minimal information provided
20	minimal	X
21	minimal	x

Overall assessment

Areas for improvement

We found a general lack of transparency and disclosure across all companies assessed, ranging from no public disclosures to minimal disclosures. Below is a summary of the public disclosures found through desktop research and as provided by the companies. Most notably, some companies do not publicly disclose whether they undertake animal testing. In the absence of explicit disclosure, it is impossible to know whether the companies undertake animal testing. However, based on their product types, geographic locations, and regulatory requirements in the locales in which they operate, it is extremely likely that many of them do engage in animal testing. Out of the companies that did acknowledge their use of animal testing the most consistent disclosure made was a discussion around compliance with the 3Rs.

A small number of companies (ranging from only one company, to less than half, depending on the question) publicly disclosed information about:

- numbers of animals used in testing over a set period;
- regulatory requirements in relation to animal testing, the legal jurisdiction in which they operate and whether they make data on alternatives to animal testing available to regulators;
- their outsourcing of animal testing to external CROs;
- consideration of non-animal approaches in procurement guidelines (or supplier codes of conduct);
- participation in company-directed independent oversight of external CROs, or details about these organisations, and their locales and associated requirements;
- participation in audit/accreditation schemes in relation to animal testing; or
- details about their development and use of non-animal approaches.

No companies on the focal list publicly disclosed:

- time-bound targets for implementing non-animal approaches or reducing use of experimental animals;
- methods used to ensure the accuracy and reliability of non-animal testing methods;
- engagement with regulators to encourage reduction of regulatory burden requiring the use of experimental animals;
- collaboration or leadership within the healthcare sector to develop and implement methods that could reduce or replace the use of animals in experimentation;
- detailed information on staff training about awareness and use of non-animal approaches; or
- information on outreach programs to inform the public about the company's commitment to reducing animal testing.

Several companies noted that the topic of animal testing was evaluated as part of their materiality assessment associated with sustainability reporting, but that the topic was determined to not be material or a particular risk to them.

Factors that influence whether and how companies are implementing alternatives

It is important to note that the types of products produced, and their stage of development will heavily influence transitions toward elimination of animal testing. For instance, companies that have long-standing product lines that no longer require early-stage research and development may not be currently engaging in animal testing. Therefore, any reduction in animal use may not have arisen because of a conscious decision to promote alternatives. Conversely, companies that make products that require animal testing to secure market entry may in principle be committed to development of non-animal approaches but find it challenging to set timebound targets given these regulatory barriers.

In addition, the jurisdiction of company location is likely to be an important factor influencing attitudes towards alternatives use. For example, companies in locales where alternatives have been encouraged or required (such as the European Union), or where animal research is closely regulated at a national level (e.g., India) were more likely to have some evidence of development of alternatives. However, it was clear that even in these scenarios, these companies were often using external CROs, and/or had subsidiaries in locations with

more permissive regulations regarding animal experimentation. It was difficult or even impossible to track and map these extended corporate relations, and their implications for companies' practices around animal testing.

Many companies with in-house labs that engage in animal testing are likely to face significant impediments to pivoting or transitioning to non-animal alternatives. For instance, investment in personnel and equipment to permit development of alternatives to animal testing is significant. Use of any particular alternative approach as a replacement for animal testing will require significant company commitment, longer-term investment, and careful planning, accompanied by supportive regulatory environments with clear standards for use of alternative approaches that do not use experimental animals.

Typical improvement opportunities

Based on the above findings, implementation of alternatives appears to be at best a medium- or longer-term objective for many companies in the health sector. It is likely that various non-animal methods will be used as adjuncts to more traditional animal-based experimentation in the short term. This use is valuable as it does contribute to reduction of animal use. These small, incremental steps support longer term goals around transitioning to alternatives by bolstering capability. They also engender public support for the company, provided the public are aware of the steps taken.

Improved transparency and engagement

There is a growing impetus amongst various non-governmental, and other advocacy organisations to emphasise 'openness' as an important norm to which ethical healthcare companies should subscribe. There are currently eight European Union countries with active transparency agreements in Europe, including France, Switzerland and the UK. Two countries outside of Europe have such agreements (Australia and New Zealand).[10] Typical components of these agreements include:

1) greater transparency about when, how and why organisations use (and continue to use) animals in research, available in a publicly accessible location;

2) enhanced communication with media and the public about their research using animals and results from it;

3) development of initiatives designed to generate greater knowledge and understanding in society about the use of animals in scientific research;

4) reporting publicly on their progress with regard to the 3Rs, including establishment of time-bound targets for replacement; and

5) sharing of experiences with others in the industry.

Even if companies do not sign on to transparency agreements, they should be strongly encouraged to use these types of standards in a rigorous and documented manner to guide their forward directions.

Companies should also explore more innovative models for increasing public engagement. For instance, in the United Kingdom, despite a long history of animal activism, many research entities host in person open days, inviting members of the public to their animal facilities, and provide 'virtual tours' of their animal units online. One company in our study noted using public tours as an engagement mechanism. Although such initiatives might be more difficult in commercial spaces, companies should consider other approaches to actively implementing openness, including involving non-governmental organisations and shareholders more actively in their practices and forward planning.

In addition, based on our findings, most companies need to be more transparent about their use of CROs for animal testing and their reasoning for using them, particularly offshore companies. In some cases, use of offshore companies may be occurring to avoid more stringent regulatory requirements in the jurisdiction where the parent company is located. Even if this is not the case, it is not an unreasonable conclusion for an external party to jump to. Companies could get on the front foot by increasing their transparency around this use to prevent such misconceptions. Where use of contractors is unavoidable, including for economic or other

[10] https://www.eara.eu/transparency-agreements; see also https://cn-bio.com/us-fda-modernization-act-2-what-does-it-mean/

reasons, companies should enact stricter oversight of these contractors and make their oversight processes explicit and transparent.

It is hard to find good examples of disclosure, and even where companies appear to be relatively transparent, there is always a risk of underlying issues that are not disclosed, in the absence of clear standards and requirements. For this reason, we hesitate to point to companies outside of our sample group as evidence of best practice.

Advocacy for change

An additional space in which companies could make significant contributions, is in relation to their advocacy activities in governmental and quasi-regulatory spaces. For instance, companies should work closely with regulatory authorities in the countries in which they operate with a view to establishing new standards for non-animal testing. Providing and sharing data on reliability on non-animal methods and advocating for adoption of these methods is a critical area for collaboration. In the United States, legislation was enacted in 2022 which states that new medicines do not need to be tested in animals to gain approval from the U.S. FDA. This is a critical change as the FDA serves as the default global regulator for pharmaceutical and related products.[11] However it is not clear how this works in practice with some efforts to use this pathway having been met with resistance. As a result, there is a formal petition for clarification pending with the FDA.[12] Consequently, it is recognised that widespread regulatory change, particularly in the pharmaceutical arena, will take significant time and financial investment, particularly in establishing standards for acceptance of non-animal testing data.

Transition to non-animal testing

Finally, companies should begin to consider their investment and development strategies associated with transitioning to non-animal testing, including training of staff, purchasing of equipment and technologies, and so on. Such transitions require establishment of priorities for transitions based on product lines and product life cycle stage, as well as the specific regulations pertaining to them. Furthermore, external support may be required to assist with upskilling in alternatives, for example from universities, non-governmental organisations, governmental research institutes, 3Rs Centres, and other private industries.

Next steps for investor engagement

We recognise that healthcare is a very popular domain for those seeking to invest ethically. In many such domains, investors can eliminate companies that do not meet ethical standards from their portfolios, or else selectively invest in companies that meet or have agreed to meet such standards. However, there is a lack of transparency about animal testing in the healthcare sector. This lack of transparency is a disincentive for anyone seeking to engage in highly targeted investment behaviours. For the investor exploring healthcare portfolios there is a high probability that the companies involved will be engaging in animal testing, even in the absence of any such disclosure.

Despite the complexities detailed in this report in relation to complete replacement of animal testing in the short- and medium-term, investors should be encouraged to engage with health-related companies on this topic. This engagement will raise the priority of this issue and support the companies in navigating towards policies around replacement of animal testing. Investors should stress that animal testing and transitions to non-animal methods are important issues to them that can materially affect their investment decisions, and the reputation of the companies in question. One important strategy is to put pressure on companies to be more transparent, in line with the types of openness principles discussed above. Such principles would not only expedite progress towards animal replacement, but promote forward planning within companies, and provide an opportunity for the companies to educate the public around barriers to replacement. Such information in turn can be used by investors to guide their approaches, providing knowledge for those who wish to avoid companies who will continue to use animal testing.

Investors should also engage with regulators and governmental organisations to encourage greater attention to establishing standards associated with non-animal testing, including development of new pathways for approvals and ongoing investment in research and development. Finally, investors should view the current

[11] https://www.science.org/content/article/fda-no-longer-needs-require-animal-tests-human-drug-trials
[12] https://www.humanesociety.org/blog/fda-petition-modernize-drug-testing.

report and similar data as providing a baseline against which ongoing research and reporting can be compared. Transitions to more limited use of experimental animals (e.g., complemented by non-animal-based testing) or elimination of animal testing in various parts of the healthcare sector will be a longer-term process which warrants ongoing scrutiny and collaboration. As part of active stewardship by ethical investors the encouragement of requirements for transparency (or milestones associated with meeting such requirements) is warranted.

Appendix A: Assessment framework/questionnaire

Questionnaire sent to companies for additional information

	All questions
1	Does your company engage in animal testing as part of operations carried out by the company itself, through subsidiaries, or use of CROs?
2	Approximately how many animals per year are used in product testing by your company, its subsidiaries or contracted research organisations? Note: this question is about estimated scale of use, not precise numbers.
3	Has the number of animals per year used in product testing by your company, its subsidiaries or contracted research organisations changed materially over the last 10 years?
4	Does your company produce products where testing on animals is mandated by an approval agency before the product can go into human clinical trials (e.g., FDA, EMA)?
5	In which legal jurisdiction(s) does this testing take place?
6	Has your company implemented any New Approach Methodologies (NAMs) that have reduced or replaced the use of animals in the last 10 years? If so for what types of research? If no, can you please explain why not. Note: we define NAMs as "as any in vitro, in chemico or computational (in silico) method that when used alone, or in concert with others, enables improved chemical safety assessment through more protective and/or relevant models and as a result, contributes to the replacement of animals."*
7	Has your company any timebound targets for implementing NAMs that could reduce or replace the use of animals? If so, how is your company tracking against these targets? If there are no targets but you have implemented NAMS, what has been the impact in terms of reducing the number of animals used?
8	Is data on alternatives, for example when run in parallel to animal testing, made available to the regulatory agencies such as FDA?
9	Does your company employ methods to ensure the accuracy and reliability of non-animal testing methods? What has worked well and what challenges have you found, if any?
10	Is your company engaged in efforts to petition regulators or similar to change requirements associated with the use of experimental animals to promote NAMs that reduce numbers of animals used? If so, what types of research and species of animals are involved.
11	In what ways, is your company collaborating or leading within the healthcare sector to develop and implement methods that could reduce or replace the use of animals?
12	Does your company have any outreach programs designed to inform the public about your commitment to reducing animal testing?
13	How are staff trained to be aware of NAMs and able to use them successfully?
14	Has your company identified any barriers to the use of non-animal methods?
15	Is your company part of any audit/accreditation schemes in relation to animal testing, for example AAALAC?

16	In relation to use of CROs for carrying out animal testing does your company incorporate consideration of NAMs in procurement guidelines?
17	In relation to use of CROs for carrying out animal testing does your company require participation in audit/assurance schemes or require some other form of company-directed independent oversight?
18	Would you consider including more data on animal testing and non-animal testing in your Annual/Integrated/ESG Reports?
19	If you have been unable to provide information for any questions due to commercial sensitivity, what are the barriers to being able to disclose this information publicly?

Questionnaire used for desktop review of publicly available information

	General questions
1	Does the company use animals for development of its products *presently* (in-house or via contract research)?
2	How does the company undertake animal testing - in-house, via contract research, or a combination of in-house and contracted? If any research is contracted, what proportion is in-house and what proportion is contracted?
3	Does the company have an explicit and publicly available policy on use of animals for research? Does this include a commitment to eliminate animal testing?
4	Which legal framework for research animal welfare do they operate under?
5	Which product approval agencies are involved for pre-market approval?
6	Does the company explicitly reference regulatory documents related to animal research and their adherence to them?
7	Does the company publicly endorse the 3Rs approach (replace, reduce, and refine)?
8	Does the company evaluate potential reputational risks associated with the use of animal testing?
9	Is the company part of any networks or coalitions focused on the 3Rs or novel alternative methodologies, or partnered with any research organisations/welfare organisations focussed on this area?
10	Has the company signed any agreements or similar about transparency, openness, or related values associated with the 3Rs or animal experimentation? (e.g., UK Concordat on Openness on Animal Research)
11	Does replacement of animal testing with alternatives have oversight within the company's governance structures and processes e.g. Board oversight, a committee that oversees animal testing, targets included in executive remuneration?
12	Does the company have a dedicated department(s) or role(s) related to animal ethics or implementation of the 3Rs?
13	Does the company have a dedicated animal care department or in-house roles inlcuding vets with appropriate advanced degrees?

13	Does the company undertake audit or participate in assurance schemes related to animal welfare?
14	Does the company engage with the media/public about their use of animals, if so how?
15	Are the company's research facilities made open for in-person tours or similar by members of the public or animal welfare groups?
16	Does the company explicitly acknowledge business or other types of risks associated with use of animals (e.g., social licence risk) or with using NAMs?
17	What metrics relating to animal testing and replacement does the company disclose, if any? For example, is data published on the numbers of animals (by species) purchased for research (both in house and by any external contractors)? Do such numbers show a decrease over the past five years?
18	Has the company been a target of animal rights activism and how have they responded to this?

	Replacement-specific questions
1	Does the company produce products where testing on animals is mandated by an approval agency before the product can go into human clinical trials (e.g., FDA, EMA)?
2	Has the company set any timebound targets for replacing animal testing with alternatives? If so, does the company regularly report progress against targets?
3	Does the company have a strategy and concrete actions to support achievement of targets, or in the absence of targets, to replace animal testing with alternatives in general?
4	Has the company financially invested over the last five years in animal testing replacement alternatives? If so, how much?
5	Has the company identified/allocated future financial investment in non-animal methods (R&D, capital or operational expenditure)? If so, how much, over what period?
6	Is there evidence that the company has replaced use of animals with non-animal methods?
7	What animal-based tests has the company stopped using in the last 10 years, and why?
8	What types of research performed by the company have transitioned to the use of non-animal testing?
9	Does the company employ methods to ensure the accuracy and reliability of non-animal testing methods?
10	Is data on alternatives, for example when run in parallel to animal testing, made available to the regulatory agencies such as FDA?
11	Is the company engaged in efforts to petition regulators or similar to change requirements associated with use of experimental animals to promote use of more novel alternative methodologies that reduce numbers of animals used?

12	In what ways, if any, is the company collaborating or leading within the healthcare sector to develop and implement methods that could reduce or replace the used of animals for testing?
13	Does the company have any outreach programs designed to inform the public about its commitment to replacement?
14	How does the company ensure that staff are aware of available alternatives and trained to use them?
15	Does the company consider NAM experience/familiarity in recruiting
16	Has the company identified barriers to the use of non-animal methods?
17	Does the company describe opportunities arising from the implementation of non-animal methods? Can the company highlight any recent innovations/ breakthroughs or advancements made using non-animal testing technologies?
18	If the company contracts animal research: does it incorporate consideration of alternatives to animal testing in procurement guidelines? Is the company working with suppliers to replace or reduce animal testing?
19	If the company contracts animal research: Does it require formal accreditation of contractors' facilities? If not, does it require audit/inspection on a regular basis, what kind of independent oversight does the company require for contractors' animal research?

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