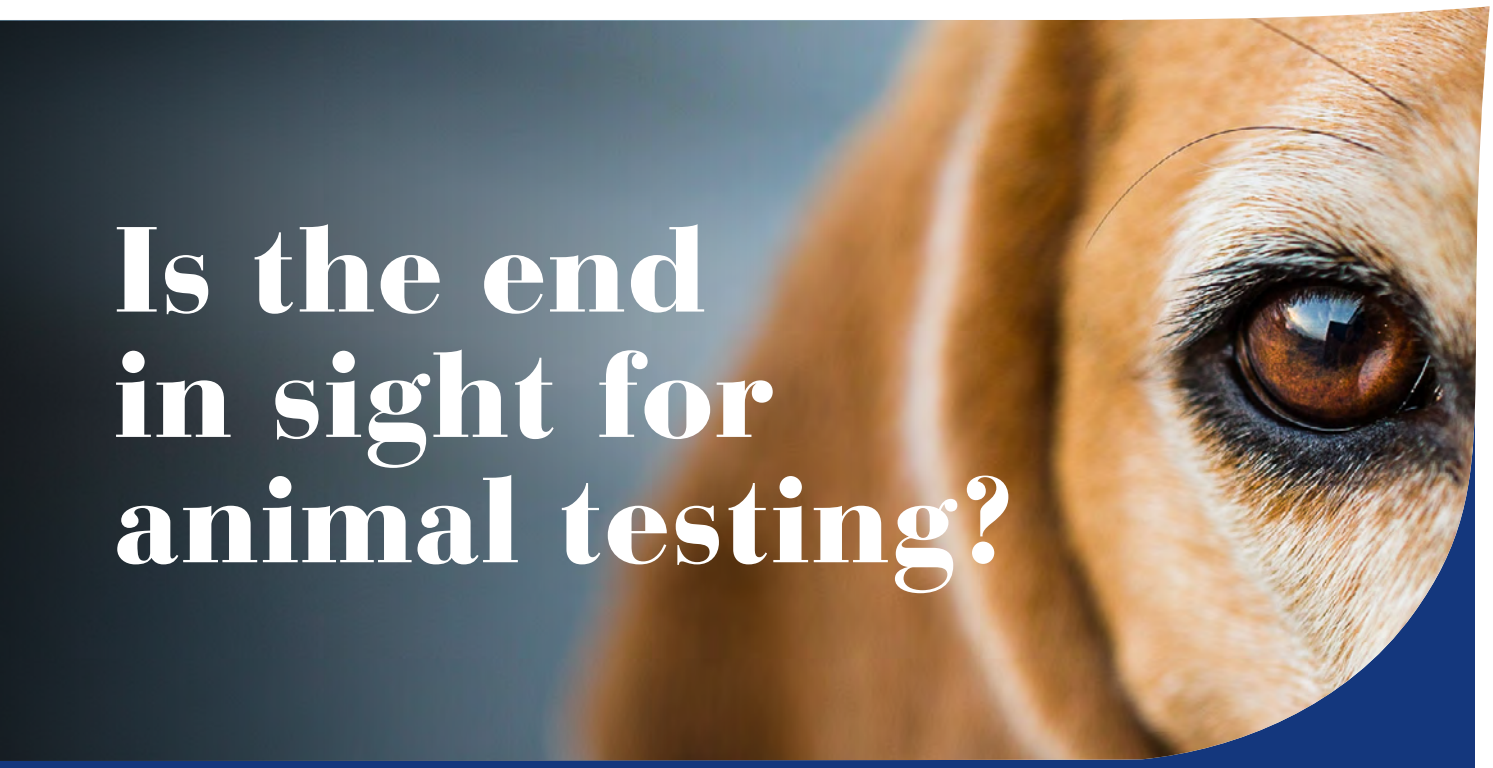

Is the end in sight for animal testing?

Animal testing is an issue that resonates with consumers and investors alike. However, investment approaches have been mainly values-based to date, and the significance of the related risks overlooked. By Ellie Higgins, Ingrid Kukuljan, and Pauline Lecoursonnois.

Setting the scene

Companies are often reluctant to disclose the extent of their involvement with animal testing. But a changing regulatory and risk backdrop, coupled with the growing advantages of alternatives, indicate that treating pharmaceutical animal testing only as an ethics-based issue is unsustainable.

Effective governance and management of pharmaceutical animal testing and preparing for a transition to alternatives are critical for the protection and creation of long-term shareholder value. Companies that welcome the integration of alternatives into their research programmes, and make investments to support the transition, will be well placed to take market share in an animal testing-free future.

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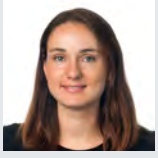

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Animal testing is a contentious issue that continues to resonate with consumers and investors, but mainstream coverage tends to focus on the ethics of the practice, and its use for cosmetic and personal care products.

Pharmaceutical animal testing is less well understood. This is where animals are used in research to develop and study the safety and efficacy of medical products in preclinical development.

While there is little remaining support for the use of animal testing in cosmetics, public opinion is divided on its application in medicine. Support tends to be contingent on the practice being carried out humanely and only where no alternatives are available.[1]

Involvement in pharmaceutical animal testing for product development exposes companies to a multitude of risks. Policy shifts in Europe and North America reflect the likelihood of a long-term phase out of the regulatory requirement for pharmaceutical animal testing, and the development, validation, and adoption of promising alternatives is well underway. Once pharmaceutical animal testing is no longer required by law or science, companies may choose to continue the practice, but at the risk of losing their social licence to operate.

EOS engages with pharmaceutical and medical devices companies on their involvement in pharmaceutical animal testing, with a focus on the three Rs: replacement, reduction, and refinement.

[1] Moral Issues | Gallup Historical Trends, Nanos Report EN (ccac.ca), Normal dot (Rev02 January 2009) (ipsos.com), Cruelty Free Europe – Animal testing in the EU – Savanta Europe, Survey report on public awareness concerning the use of animals in scientific research in Japan (jst.go.jp)

We want companies to have robust governance and risk management structures where testing must continue, and to leverage opportunities created by the alternatives transition, to drive long-term value creation.

Global policy perspectives

Pharmaceutical animal testing requirements exist to some extent in all developed markets, but vary greatly by region. The use of alternatives in pharmaceutical research is considered standard practice in the EU and UK, and animal use is only permitted where its scientific necessity can be demonstrated. In 2021, the European Parliament called for the development of an EU-wide action plan to phase out requirements for animal testing under chemicals legislation, which includes coverage of human and veterinary medicines. The European Commission announced its intention to accelerate this phase-out in 2023.[2]

The North American market is still in the early stages of its alternatives transition, but the changes are palpable. Legal protections for animals used in pharmaceutical research, and funding for alternative technologies, have steadily increased in recent years. In 2023, the Food and Drug Administration (FDA) Modernization Act 2.0 was enacted in the US, removing several longstanding requirements for drugs to be tested on animals where certain alternatives are available.[3] Although the replacement of animals in the product development process is still treated as the exception, not the rule, its introduction incentivises companies to reduce their reliance on the practice.

Other countries, such as China and Japan, acknowledge the importance of the three Rs within regulatory regimes but continue to require animal testing in pharmaceutical product development. Asian governments' approaches to ensuring laboratory animal welfare and safety are also known to be less stringent than those of the Western world.[4]

The lack of global harmonisation has led to inconsistency and redundancy, hindering any single region's efforts to move towards alternatives. However, recent approvals of animal-free pharmaceutical research strategies by intergovernmental bodies such as the OECD should help to improve standardisation of the alternatives allowed in the future.[5]

The changing risk landscape

Pharmaceutical research is commonly performed on rodents and fish, but rabbits, dogs, cats, non-human primates, and other animals are also used. Recent events regarding the use of non-human primates (NHPs) demonstrate the risks.

The price per animal for NHPs rose from roughly US$5,000 in 2020 to $30,000 in 2023 due to a shortage driven by China's export ban.[6] The country was previously the largest exporter of NHPs worldwide. The NHP shortage threw a spanner into drug development pipelines at the onset of the Covid-19 pandemic and continues to cause study delays on a global scale. After receiving subpoenas in connection with a federal investigation of an NHP smuggling operation, the share prices of two major US contract research organisations – Charles River Laboratories and Inotiv – tumbled.[7,8]

While sourcing complications are possible with any product, they are particularly problematic for live animals, as life-sustaining care and facilities must be provided throughout the supply chain. Animals are transported from specialist breeders and must remain healthy and in highly-controlled environments to produce reliable results.

Failure to maintain the appropriate conditions during transport and at research facilities can have a major impact on the health of animals and their suitability for research. Companies found in violation of laws relating to laboratory animal welfare may lose external funding, face facility shutdowns, or incur other legal and financial penalties.

The potential for damage to a company's social licence to operate is more tangible with animal testing for cosmetics, or farm animal welfare. Consumers dissatisfied with a company's animal use practices can easily change their shampoo or fast-food selection. However, anonymity granted to companies through the use of contract research organisations for pharmaceutical animal testing, and patent exclusivities in medical products, create challenges for consumers seeking to identify or boycott brands based on their treatment of animals.

The societal backlash regarding pharmaceutical animal testing is perhaps best illustrated by the US government seizure of thousands of beagles from an Envigo breeding and research facility due to welfare concerns in 2022. In 2024, Envigo's parent company was ordered to pay a fine of over US$35m, the largest in US history for an Animal Welfare Act case.[9]

[2] Texts adopted – Plans and actions to accelerate a transition to innovation without the use of animals in research, regulatory testing and education – Thursday, 16 September 2021 (europa.eu), Commission acts to accelerate phasing out of animal testing (europa.eu)
[3] Top national pharma markets by market share 2022 | Statista, S.5002 – 117th Congress (2021-2022): FDA Modernization Act 2.0 | Congress.gov | Library of Congress
[4] Legislation & Regulation In Asia | FRAME
[5] World's first toxicology testing strategy without animal testing adopted by OECD | Givaudan
[6] Monkey Business Threatens U.S. Drug Discovery – WSJ
[7] Animal Testing for Vaccines Relies on a Cruel Monkey Supply Chain (bloomberg.com)
[8] https://www.washingtonpost.com/science/2023/03/01/monkeys-cambodia-research/
[9] Office of Public Affairs | Animal Breeder Pleads Guilty to Animal Welfare and Pollution Crimes and Will Pay More than $35M, Including Record Fine in an Animal Welfare Case | United States Department of Justice

Nature-related impacts – species under threat

The impacts and dependencies relating to animal testing should be considered as part of a company's biodiversity strategy. While some animals used in testing appear to be in abundant supply, the same cannot be said for other animals commonly used in pharmaceutical research.

Following China's export ban on non-human primates (NHP), a rapid shift in sourcing locations occurred, contributing to major increases in NHP poaching. In 2022, the International Union for Conservation of Nature (IUCN) issued endangered status to one species of NHP frequently used in pharmaceutical animal testing, the long-tailed macaque. Hunting and trapping were previously a threat to the population and poaching has become rampant due to the heightened demand and price. The species is also threatened by habitat deforestation and degradation.[10]

Horseshoe crabs are used in pharmaceutical animal testing due to the properties of their distinctive blue blood. The crabs are typically caught and released back into the sea after a portion of their blood has been extracted, but improper handling and aftercare techniques are common, putting their continued livelihood at risk. The American and tri-spine horseshoe crabs are classified as vulnerable and endangered by the IUCN, respectively. Horseshoe crab eggs are also a food source for fish, birds, and other wildlife, and their shells serve as a habitat for smaller species.[11]

Notably, Eli Lilly has made a formal commitment not to use any NHP species classified as endangered or that are caught in the wild. The company is an advocate for alternatives to horseshoe crab-derived blood reagents and has converted 80% of its testing to a synthetic alternative since 2016.[12]

What alternatives can be used?

Some 90% of drugs that pass preclinical tests ultimately fail, and the biological differences between animals and humans are known to be a contributing factor.[13] The technological evolution in drug testing and alternatives, which can deliver more accurate and efficient results, creates opportunities to switch, to the benefit of society and animals.

Alternatives to pharmaceutical animal testing fall into three segments – those performed using biological molecules (in chemico), those using computational modelling (in silico), and those using cells outside the body (in vitro).

Many alternatives are more efficient, cost-effective, accurate, and relevant to human biology than animal-based research. These advantages are crucial, as alternatives must compete with, and outperform animal-based research to gain confidence and support from industry and regulators.

Major pharmaceutical brands are now partnering with innovators in the alternatives space, as well as investing in alternative technologies development in-house. Even contract research organisations, considered to be the largest proponents of animal testing, have acknowledged the need to reduce their reliance, and are allocating resources to alternatives development and integration.[14]

Many alternatives are more efficient, cost-effective, accurate, and relevant to human biology than animal-based research.

[10] Macaca fascicularis (Long-tailed Macaque) (iucnredlist.org), Animal Testing for Vaccines Relies on a Cruel Monkey Supply Chain (bloomberg.com)

[11] International Horseshoe Crab Day: a celebration of the flagship species for coastal habitat conservation | IUCN, Pharmaceutical labs bleed horseshoe crabs for vaccines with little accountability : NPR

[12] Environmental | 2023 Sustainability Report | Eli Lilly and Company, Animal Care and Use | Discovery | Science | Eli Lilly and Company

[13] Why 90% of clinical drug development fails and how to improve it? – PMC (nih.gov)

[14] Charles River Laboratories Launches Alternative Methods Advancement Project to Reduce Reliance on Animal Testing | Charles River Laboratories International, Inc. (criver.com), Envigo expands R&D capabilities in non-animal technologies to meet regulatory and market requirements for in vitro assays (inotivco.com)

[15] Merck KGaA, Darmstadt, Germany and Quris-AI Expand (globenewswire.com)

[16] How science is getting closer to a world without animal testing (ft.com)

Despite these efforts, the alternatives market is not yet mature enough to support a total elimination of pharmaceutical animal testing without compromising the integrity of the product development process. To advance the alternatives transition, companies will need to work diligently and collaboratively on technology development and validation, in concert with regulators.

In silico alternatives

Artificial intelligence (AI) is helping to reduce, refine, and in some cases, replace animal testing. By ingesting vast quantities of human health data and running modelling scenarios, researchers may be able to screen a drug for its applicability to humans more effectively and quickly than by testing it on animals first.

For example, Merck KGaA has formed a partnership with Quris-AI on its AI platform for clinical prediction, and has seen success in its ability to detect drug toxicity in comparison with in vitro and animal-based methods.[15] Merck is a leader in transparency regarding pharmaceutical animal testing and has made a formal commitment to phase out its use of the practice. AstraZeneca has also implemented AI technologies that have significantly reduced the rate of failure in the first phase of human trials.[16] EOS continues to engage in the healthcare space to ensure that AI models are used responsibly and with proper controls in place to eliminate bias.

Our engagement approach

EOS has historically engaged on animal welfare with companies in the agriculture and animal health industries. We have also collaborated with the FAIRR investor network on various initiatives relating to livestock production. In our Q3 2021 Public Engagement Report, we outlined the threats posed by antimicrobial resistance and our engagement approach across the animal protein supply chain.[17]

Based on recent changes in policy surrounding pharmaceutical animal testing and the growing risks and alternatives opportunities, we have scaled up our engagement with companies in the pharmaceutical and medical device sectors to protect and enhance shareholder value and drive progress towards the alternatives transition.

- **Replacement, reduction, and refinement**

  Replacement, reduction, and refinement (the three Rs) form the underlying framework for present-day approaches to more humane pharmaceutical animal testing.[18] We ask companies to formally commit to these principles and to demonstrate the outcomes from each. Where pharmaceutical animal testing must continue for some purpose, be it regulatory, scientific or otherwise, we expect companies to provide reasonable transparency and accountability on the rationale and extent of their involvement.

- **Risk management**

  We ask for evidence of robust governance and management structures in place extending across the pharmaceutical animal testing value chain to ensure implementation of the 3 Rs, and that all animals are kept in appropriate conditions and treated humanely. This should include information on due diligence practices, global sourcing risk management strategies, and a clear pathway of escalation to the board where critical concerns arise.

- **Alternatives investment and policy engagement**

  As the final component of our engagement strategy, we urge companies to prepare for and facilitate the alternatives transition. We seek evidence that companies are allocating capital to alternative technologies development and collaborating with peers for innovation to challenge the market norms. They should also advocate for the harmonisation of legal requirements for animal pharmaceutical testing and the acceptance of alternative technologies wherever feasible.

Looking forward, we expect companies to leverage the opportunities for growth created by the alternatives transition to drive long-term shareholder value. EOS will monitor the developing geopolitical complexities around animal sourcing and other related risks. And we will pay close attention to how North American pharmaceutical companies can further enact their 3 Rs commitments in response to the FDA Modernization Act 2.0.

[17] EOS Public Engagement Report (hermes-investment.com)
[18] The 3Rs | NC3Rs

CASE STUDIES

Johnson & Johnson and Pfizer

At the end of 2023, EOS wrote to a group of companies in the healthcare and pharmaceutical space urging them to voice their support for Chapter 86 during the open consultation period at US Pharmacopeia. Chapter 86 relates to the use of alternatives to reagents derived from horseshoe crabs in certain tests.[19]

Following this outreach, we held several dedicated calls with a range of different pharmaceutical companies to discuss their use of animals in research. As part of this engagement approach, we met with Johnson & Johnson's global head of animal welfare to discuss the company's approach.

This included asking about the board's role in overseeing pharmaceutical animal testing and its due diligence process for sourcing and contract research organisations. We were pleased to learn more about how the company collaborates with peers to share leading practices and brings real use cases to regulators to advance the approval of alternatives.

In conversation with subject matter experts at Pfizer, the company explained how it considers pharmaceutical animal testing within the framework of its environmental strategy, and noted its work to reduce its use of horseshoe crab-derived reagents. It said that it continues to examine new opportunities for alternatives integration and referenced its leadership's involvement with the work on Chapter 86.

We encouraged both companies to leverage the opportunities created by the FDA Modernization Act 2.0 to accelerate their efforts toward the 3 Rs. We asked each to demonstrate the outcomes of their efforts to stakeholders, such as through case studies of successful alternatives integration, to give examples of peer collaborations, and to publish data to reflect trends in animal usage over time.

CASE STUDY

Sanofi

At Sanofi, we met with the company's chief veterinary officer for a dedicated animal testing discussion in 2024. The company has a target to reduce the number of animals used in research and testing by 50% between 2020 and 2030.[20]

He provided some reassurance that the company is on track to achieve this target, and this is supported by the use of various alternatives and digital replacement technologies. He also confirmed that this target applies to the animal testing performed in the company's own operations and through contract research organisations (CROs), but noted that it has faced difficulties in some geographies to ensure that all animals are accounted for.

> **The company's policy is not to use endangered primate species, and the chief veterinary officer believes the industry should prepare for a potential complete ban on the use of non-human primates.**

It was positive to hear that relationships with CROs have been ended in the past where remediation efforts were unsuccessful. The company continuously assesses the financial impact of potential regulatory and market changes and works to minimise its dependency on animal testing.

The company's policy is not to use endangered primate species, and the chief veterinary officer believes the industry should prepare for a potential complete ban on the use of non-human primates. We encouraged expanding this commitment to any endangered species. The company stated that it monitors animal populations in its supply chain closely and makes efforts to reduce the use of vulnerable animals such as horseshoe crabs.

Finally, we encouraged the company to publicly demonstrate how it uses its influence to drive industry-wide change through engagement with peers and regulators.

[19] Bacterial Endotoxins Test Using Recombinant Reagents | USP-NF (uspnf.com)

[20] https://www.sanofi.com/assets/dotcom/content-app/documents/Animal-Protection.pdf

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