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Office of Science and Technology Policy
Executive Office of the President

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Accelerating the American Scientific Enterprise
Docket ID: OSTP-TECH-2025-0100

Dear Office of Science and Technology Policy leadership:

I'm writing on behalf of People for the Ethical Treatment of Animals—PETA entities have more than 10 million members and supporters globally, and PETA U.S. is the largest animal rights organization in the world—to recommend federal policy updates that that will accelerate the American scientific enterprise, enable groundbreaking discoveries, and ensure that scientific progress and technological innovation benefit all Americans.

Broadly, policies for the conduct and funding of human health-related research and regulatory testing should mandate that these activities be performed using non-animal, human-relevant tools and technologies. These include, but are not limited to, human *in vitro* models such as organs-on-chips and organoids, human-based mathematical and computational models, human tissue models, multi-omics research, and advanced imaging. To increase their power, these tools can be augmented with artificial intelligence (AI), allowing for the development of digital twins, systems biology models, and multi-scale simulations that allow scientists to explore mechanisms in ways that exceed the accuracy and translation of outdated and fundamentally flawed tests and experiments on animals.

Enforceable mandates and standards are needed to safeguard recent advances

In 2025, PETA and its supporters welcomed long-overdue science policy advancements at federal agencies. On April 10, the Food and Drug Administration (FDA) announced plans to phase out animal testing requirements for drugs, including the development of monoclonal antibodies.[1] This policy change has the potential to spare tens of thousands of animals each year. PETA scientists have done groundbreaking work in this area, including funding the development of non-animal antibodies to fight infection. On December 2, the FDA went further, calling on the pharmaceutical industry to propose tests to replace primates and other animals in experiments.

Entities
- PETA Asia
- PETA India
- PETA France
- PETA Australia
- PETA Germany
- PETA Switzerland
- PETA Netherlands
- PETA Foundation (U.K.)

On April 29, the National Institutes of Health (NIH) announced a shift as well, pledging to prioritize cutting-edge, non-animal research methods and reduce funding for animal experimentation.[2] NIH's plan adopted several recommendations from PETA scientists' strategy to phase out animal use, *Research Modernization NOW*,[3] including expanding funding, training, and infrastructure for non-animal methods. NIH has since taken actions toward this goal, including closing its in-house beagle laboratories, cutting funding for animal experiments, disallowing funding opportunities for animal-only experiments, launching new centers and projects to advance animal-free science, and permitting grant funds to be used for animal rehoming and retirements.

The Environmental Protection Agency, Navy, and Coast Guard have also made advancements toward reducing animal use.

While these developments mark meaningful progress, they remain voluntary and lack the force of law. Without binding regulations, clear benchmarks, and accountability measures, these commitments could stall—or even be reversed—under future administrations. To safeguard the critical mission of moving toward human-centric science and ensure these developments have lasting impact, federal agencies must be held to enforceable standards that guarantee timely implementation and measurable outcomes.

Scientific and cultural shifts demand reform

Every year, more than 110 million animals are confined in U.S. laboratories.[4] Some are treated like breeding machines, many are subjected to physical and psychological torment through invasive experimentation and testing, almost all are killed. Public opposition to the use of animals in experiments has increased steadily. In 2025, Gallup reported that 53% of Americans felt that medical testing on animals was morally unacceptable, up from 34% in 2005.[5] This cultural shift may be attributed, in part, to increasing awareness of animal sentience and advancements in non-animal research and testing methods that are now able to supplant their use.

A great deal of scientific research in the last several decades shows that experiments on animals are flawed and divert both monetary and intellectual resources from more reliable and relevant methodologies. Intrinsic biological and genetic differences among species contribute significantly to inescapable problems in extrapolating results from animals to humans, even in the best controlled and best executed study designs. The following statistics illustrate this point:

- 95% of new drugs fail in human clinical trials,[6] despite having passed safety and efficacy testing in animals.
- 90% of basic research, most of it conducted on animals, does not enter routine clinical use within 20 years.[7]
- Up to 89% of preclinical studies—equating to $28 billion per year—cannot be reproduced.[8]
- 81% of the time, animal tests fail to detect the potential side effects of drugs in humans.[9]

By mandating a move away from experiments on animals and toward advanced, human biology-based scientific methods, the federal government can advance biomedical research, rapidly expand job growth in science and technology, and reduce healthcare costs for all Americans. Without these reforms, the U.S. biomedical and regulatory science enterprise will fail to provide the discoveries and applications needed to protect human health and the environment.

Recommendations in response to specific prompts in this Request for Information

(i) What policy changes to Federal funding mechanisms, procurement processes, or partnership authorities would enable stronger public-private collaboration and allow America to tap into its vast private sector to better drive use-inspired basic and early-stage applied research?

Broad changes to federal funding mechanisms to modernize basic and applied research

To drive use-inspired basic and applied human-relevant and reproducible research, the Office of Science and Technology Policy (OSTP) should implement a new policy disallowing the use of animals in federally funded research unless the research is for the direct benefit of the individual animals or species involved (e.g., veterinary or conservation studies). In such cases, the research should meet the following criteria:

- Adherence to human subject-level protections such as informed consent principles that can be agreed upon by a designated representative representing the animal(s)' well-being and dignity
- Ethical and harm-benefit review by an independent committee that includes individuals with expertise in animal welfare
- Clear and transparent justification of the research's benefits to the individual animal(s) or species.
- Demonstration that no scientifically valid species-relevant alternative, such as an animal organ-on-chip system or AI-based model, can be used to answer the research question(s) or meet the regulatory requirement(s)

Federal funding is a finite resource. When animal use is rewarded with public funds, innovation toward human biology-based science remains stalled. A mandate for human-centric science is needed to overcome entrenched institutional and technological lock-in, as the continued use of animals is based more on tradition than its potential to result in meaningful advances for human health or the environment.

Additional recommendations

- Create public-private consortia where companies, academics, and government researchers collaborate on the development and validation of non-animal, human-relevant models.
- Ensure grant review criteria are tailored to non-animal methods. The National Institute of Environmental Health Science's Interagency Coordinating Committee on the Validation

of Alternative Methods' (ICCVAM) "Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States" highlights practical pathways to accelerate the use of 21st-century science, including grant review criteria tailored to non-animal methods—such as *in vitro* assays, microphysiological systems, and *in silico* models—that better reflect human biology, metabolism, and physiology and are demonstrably reproducible.[10] Because most grant review processes are still optimized for animal-based research, federal funding mechanisms should be re-defined to appropriately distribute support to non-animal methods. For example, non-animal-specific clauses can be added to federal solicitations and procurement (e.g., Broad Agency Announcements (BAAs) and Requests for Proposals (RFPs)). See also response to *(v)*: Animal methods bias in grant review must be investigated and mitigated to reduce barriers to nonanimal methods uptake.

- Offer funding mechanisms that allow researchers currently using animals to modernize their laboratories for the use of non-animal, human-relevant technologies. Incentivize collaboration with the private sector to facilitate retraining and modification of these technologies to meet the needs of individual researchers and their teams.
- Broaden NIH's ability to use Other Transaction (OT) awards for applied research partnerships focused exclusively on non-animal methods and tools. OT awards allow NIH greater flexibility to engage new partners, or engage existing partners in new ways, and could foster more private sector relationships to speed the development and validation of these technologies.
- Prioritize cooperative agreements for technologies that replace animal use, offering advantages to those that include commercialization and regulatory validation plans.
- Facilitate agency procurement of validated non-animal platforms for intramural research programs so that federal purchasing power can boost industries developing these technologies, create early markets, and encourage private investment.
- Establish public, shared-use facilities for non-animal, human-relevant technologies to lower costs for small businesses and academics while ensuring standardization and reproducibility.
- Offer tax or credit incentives tied to federal partnership programs for companies investing in and/or using non-animal technologies.
- Mandate FAIR (Findable, Accessible, Interoperable, and Reusable) data standards and centralized repositories for federally funded research, including for validation studies. Provide public access to these resources to reduce duplication.
- Update procurement processes to ensure reproducible reagents are used in research. Replacing animal-derived ingredients (e.g., animal-based serums, media components, and antibodies)—a major source of variability in studies—will improve robustness. Programs

designed to catalyze use of non-animal methods (e.g., NIH's Complement-ARIE) should include the additional funding needs to develop non-animal reagents if they do not already exist, across all funded activities.

- Establish outcome-based grants. Tie funding to regulatory applicability (e.g., research that will directly support a regulatory agency in the development of guidance on and in the acceptance of modern, non-animal test methods), not just publications.
- Incentivize regulatory submissions (e.g., Investigational New Drug (IND) applications, pesticide registrations) that incorporate non-animal methods, for example by priority review or reduced user fees.

(ii) How can the Federal government better support the translation of scientific discoveries from academia, national laboratories, and other research institutions into practical applications? Specifically, what changes to technology transfer policies, translational programs, or commercial incentives would accelerate the path from laboratory to market?

Amend the Bayh-Dole Act

- **Create a statutory preference for non-animal technologies:** Like its advantages for small businesses or universities, and U.S. manufacturing, giving licensing preference to patent applications that do not involve animal use and to entities who invest in the development and validation of non-animal methods would shift commercialization incentives toward human-relevant models and encourage companies and universities to adopt non-animal methods. Similar preference could be given to entities that explicitly pledge to reduce animal use.
- **Permit royalty relief for technologies that can replace animal use:** Reduce or waive royalties and upfront fees for licensees using non-animal technologies.
- **Mandate transparency and replacement planning:** To promote transparency and prevent publicly funded IPs from remaining entrenched in animal-based paradigms, where applicable, licensees should be required to publicly report on their use of animals and reduction in animal use.
- **Add non-animal progress metrics to iEdison reporting:** In addition to reporting development stage and other information, adding metrics to assess an invention's potential for reducing animal use will enable agencies to track translation quality and progress toward this goal.

Additional recommendations

- Facilitate intellectual property (IP) and collaboration agreements across federally funded institutions to accelerate partnerships for non-animal, human-relevant technologies.

- **Expand infrastructure for animal-free science.**
    - Expedite NIH's Standardized Organoid Modeling Center.
    - Scale National Center for Advancing Translational Science's (NCATS) Tissue Chip for Drug Screening program and expand its remit to facilitate tissue chip work in basic research and disease modeling.
    - Expand NCATS' Clinical and Translational Science Awards (CTSA) Program and prohibit awardees from using animals in preclinical science. Provide support for reproducibility and good laboratory practice (GLP) to shorten the path from preclinical to clinical trials. Develop similar programs at the Department of Veterans Affairs and other agencies that provide external funding for preclinical research.

- **Fund priorities outlined in work plans or roadmaps from agencies.** Agencies have identified priorities to advance human health protection via roadmaps, but progress is substantially slowed without adequate funding and personnel to carry out the activities proposed within these roadmaps. For example, the FDA's 2017 *Predictive Toxicology Roadmap*[11] and the EPA's 2021 *New Approach Methodologies Work Plan: Reducing Use of Vertebrate Animals in Chemical Testing*[12] outlined essential activities to advance science and human health research and funding is needed to address the objectives within.

- **Ensure sustained follow-up.** Some agencies have made significant progress implementing new test methods, but long periods without follow-up leave outcomes unclear. For example, in 2012, the United States Department of Agriculture (USDA) co-sponsored an Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) workshop to identify opportunities to replace hamsters in evaluating veterinary leptospirosis vaccines. Over the subsequent decade, animal use was reduced by approximately 55% as manufacturers adopted USDA-led policy changes. Nevertheless, about 15,000 hamsters per year are still used, and plans to revisit the 2012 goals remain unclear. Agencies should ensure that long-term plans are followed up on to facilitate uptake or modern test methods.

- **Address review bottlenecks.** At the FDA and EPA, progress is sometimes delayed by unnecessarily lengthy internal reviews (e.g., upper-management clearance for coauthored publications or policies in final stages) and unclear or limited paths to reach the appropriate decision-making experts within the agencies. Agencies should implement internal timelines and guidelines to facilitate timely review so advancement of new approaches is not stalled and animal use does not continue despite analyses showing that they lack scientific value. These internal guidelines should identify the specific agency staff in charge of decision-making regarding the path from laboratory to market and ensure those staff have the ability to prioritize these tasks.

- **Create regulatory incentives.** Offer priority reviews or reduced user fees for data packages built on non-animal methods.
- **Provide templates and quality systems.** Clear templates and lab quality systems reduce friction transitioning from bench to regulatory decisions.
    - Standardized modules for assay description, applicability domain, performance (sensitivity/specificity), uncertainty, and defined-approach decision logic, where applicable, provided within templates by agency would provide guidance for non-animal method dossiers.
    - Expand translational programs (e.g., NCATS pilot calls) to fund Organisation for Economic Co-operation and Development (OECD) Good In Vitro Method Practice (GIVIMP)[13] certification audits for academic labs, providing translational direction and enabling reliable data packages for regulatory review.
- **Incentivize defined reagents** (e.g., antibodies, cell culture media, extracellular matrices). Animal-derived reagents are biological products of unknown and variable composition and a potential source of biological contamination. Animal-free, defined reagents are known in chemical composition and purity and meet specific, standardized quality parameters. Defined reagents improve reproducibility and reduce variability—critical for moving discoveries from research to regulatory acceptance and commercial use. Federal support could include:
    - Funding incentives for projects that adopt defined reagents.
    - Technology transfer programs to scale production and distribution of sequence-defined antibodies, chemically-defined media, and other defined reagents.
    - Commercial incentives for companies that standardize animal-free reagents and make them broadly accessible.

(iii) What policies would encourage the formation and scaling of regional innovation ecosystems that connect local businesses, universities, educational institutions, and the local workforce—particularly in areas where the Federal government has existing research assets like national laboratories or federally-funded research centers?

Standardize materials and skills by:

- Establishing centers analogous to the NIH Standardized Organoid Modeling Center for other advanced methods, such as organs-on-chips and defined testing approaches.
- Developing regional centers or systems for characterizing or sharing data on defined reagents.

- Funding Organisation for Economic Co-operation and Development (OECD) Good In Vitro Method Practice (GIVIMP)[14] coursework and OECD Test Guideline training (e.g., skin/eye irritation, skin-sensitization defined approaches) at colleges and universities.

(iv) How can Federal policies strengthen the role played by small- and medium-sized businesses as both drivers of innovation and as early adopters of emerging technologies?

- Create non-animal method-focused SBIR (Small Business Innovation Research) and STTR (Small Business Technology Transfer) tracks with set-aside funds for Small and Medium-sized Enterprises (SMEs) building organoids/organ-on-chip, computational toxicology tools, and other non-animal approaches; include fast-track Phase II if a tool enables replacement of a vertebrate test.
- Establish federal purchasing commitments for SMEs providing materials used within non-animal methods (e.g., reconstructed human epidermis).
- **Clarify regulatory acceptance of methods.** For example, the FDA should enact a policy to clarify acceptance of the use of *in vitro* reconstructed human tissue models for assessing skin irritation potential of medical device extracts that have been extensively validated, are included in an International Organization for Standardization (ISO) standard, and are accepted by the European Union member states, Australia, Japan, and China.
- **Improve execution of agency programs that connect with businesses.** For example, the Center for Devices and Radiological Health's (CDRH's) Medical Device Development Tool (MDDT) program was a welcome addition in 2013, promising to overcome roadblocks to the timely qualification of new tools to better protect public health. Yet, more than a decade later, the program is far from meeting expectations. The number of MDDT submissions is unknown as it is not public information; however, there has yet to be an *in vitro* method approved to replace an animal test and submissions have been fraught by reviewer turnover, inconsistent feedback, endless quests for data, and ever higher bars to reach with no emphasis from the agency on the most efficient path to qualification.
- Operationalize the Interagency Coordinating Committee on the Validation of Alternative Methods' (ICCVAM) strategic goal to connect end users with non-animal method developers by identifying and communicating needs, influencing funding distribution, and collaborating with industry stakeholders to encourage open dialogue.[15] To implement, agencies could:
    - Develop a standard submission process for pre-submission meetings and feedback.
    - Publish a public list of reference chemicals.

- Provide FAQs detailing regulatory needs and data expectations for method approval.
- Follow the example of the ICCVAM Acute Toxicity Workgroup[16] project that engaged numerous stakeholders to develop *in silico* models of acute oral systemic toxicity.

(v) What empirically grounded findings from metascience research and progress studies could inform Federal grantmaking processes to maximize scientific productivity and increase total return on investment? Please provide specific examples of evidence-based reforms that could improve funding allocation, peer review, or grant evaluation.

Meta-research on model validity is urgently needed to inform evidence-based funding decisions

A major shortcoming of existing federal grantmaking processes is that decision-making is not based on systematic evaluations of model utility or demonstrated research gaps.

Several U.S. funding entities, including NIH, the Department of Veterans Affairs, and the Department of Defense, are members of the Ensuring Value in Research Funders' Forum (EViR), a collection of prominent international funding bodies formed to address waste in clinical and preclinical research. EViR lists among its guiding principles that, "[t]o fund research that is high-quality and addresses unmet needs, funders should require that there is an evidence gap demonstrated by a review done systematically. Research methods should be appropriate and robust with ability to replicate findings."[17]

Human health-related studies conducted without reference to what is already known—whether the study has been done previously or whether the methods used provided actionable answers relevant to human health—risk wasting resources through redundant or inapplicable work. Before releasing public grant money, funders should be consistently evaluating whether a thorough review of the evidence has been conducted and whether its findings justify the need for the proposed study or the use of the proposed model.

Yet a cursory look at federally funded projects demonstrates that awarding agencies are undertaking no such reviews. There is no concerted effort within the U.S. federal government to put this recommendation into action.

For research areas in which there is still some question as to whether the use of animals is beneficial, a thorough systematic review should be conducted to determine the utility of using animals for this purpose. Systematic reviews, which critically analyze multiple research studies, are a crucial first step in assessing the effectiveness of animal use. Such systematic reviews should include information about the return on investment received by the public from the results of animal studies, particularly when they have been publicly funded.

The act of conducting a systematic review can itself strengthen biomedical research quality, with a Dutch case study showing that researchers who received systematic review training became strong advocates for its use and improved the rigor and transparency of their own research.[18]

Animal methods bias in grant review must be investigated and mitigated to reduce barriers to nonanimal methods uptake

Decades of scholarship on research evaluation have illuminated the role that norms and bias have on research evaluations, including in the context of funding. Because animal use is deeply embedded in institutional culture, established animal experimenters have accumulated disproportionate power, reinforcing a conservative status quo that privileges familiar approaches and marginalizes newer methods regardless of their potential, a dynamic consistent with the "Matthew Effect"[19] and "cognitive particularism."[20] Extensive evidence demonstrates that such biases suppress innovation and discourage risk-taking.[21,22,23] Together, this body of research indicates that animal methods bias, defined as a preference for animal-based methods or lack of expertise to properly evaluate non-animal methods, is likely systemic, and that meaningful change in research grant evaluation is urgently needed.

Though the quantity of evidence on animal methods bias in grant funding is limited so far, one recent analysis revealed a potential bias toward animal-based methods in study sections tasked with reviewing NIH grant applications for basic, translational, and preclinical neuroscience research. The study showed that the expertise of these study sections was predominantly weighted toward animal use, and that the greater the animal-based expertise on the study section, the fewer non-animal grants were awarded.[24]

OSTP should act on the authors' recommendations for further research and strategies to mitigate this bias and compel funding agencies to:

- Conduct internal studies (and/or enable external meta-research) to quantify animal methods bias in grant review and encourage applicants to report any experiences with it
- Ensure experts in nonanimal methods are present on all panels reviewing applications for basic, preclinical, and translational research, as well as toxicological assessment.
- Create funding avenues specific to nonanimal research
- Consult the Coalition to Illuminate and Address Animal Methods Bias (animalmethodsbias.org), an international collaboration that is at the forefront of work on this issue and may have additional recommendations.

Employ lottery systems to fund human-relevant technology breakthroughs

Evidence from metascience shows that employing lottery systems in funding decisions may reduce bias and encourage risk-taking. For non-animal research-focused grant calls, agencies could screen applications for rigor and feasibility and then allocate funding via lottery to overcome the conservatism in peer review that favors entrenched animal-based paradigms. Awardees could be asked to meet short-term milestones, such as demonstrating validation against human clinical data, to show progress and accountability.

Additional recommendations

- Agencies should embed human-relevance criteria in peer review, explicitly advantaging proposals that replace or significantly reduce animal use and demonstrate human relevance.

(vi) What reforms will enable the American scientific enterprise to pursue more high-risk, high-reward research that could transform our scientific understanding and unlock new technologies, while sustaining the incremental science essential for cumulative production of knowledge?

Create dedicated high-risk funding streams for human-relevant methods

Many traditional federal funding mechanisms favor incremental, low-risk projects that rely on entrenched methodologies such as animal use. Newer, non-animal methodologies, despite their demonstrated success and potential, therefor face the hurdle of conservatism during grant peer review. Establishing agency-wide transformative and disruptive, non-animal research programs, similar to the NIH's Director's Pioneer and New Innovator Awards would fund high-risk, high-reward research aimed at replacing animal models with these advanced platforms.

Additional recommendations

- Launch Defense Advanced Research Projects Agency (DARPA)[25] like new approach challenges targeting the development of non-animal test batteries linked to adverse outcome pathways (AOPs) for complex endpoints (e.g., developmental neurotoxicity, inhalation).
- Invest in centers like the NIH Standardized Organoid Modeling Center for other new approaches such as organs-on-chips. See also responses to:
    - *(i)* Facilitate agency procurement of validated non-animal platforms for intramural research programs so that federal purchasing power can boost industries developing these technologies (particularly when they are high-risk/high-reward), create early markets, and encourage private investment.
    - *(v)* Employ lottery systems to fund human-relevant technology breakthroughs

(vii) How can the Federal government support novel institutional models for research that complement traditional university structures and enable projects that require vast resources, interdisciplinary coordination, or extended timelines?

Establish interagency centers to co-author acceptance guidance and run joint regulatory pilots (e.g., skin-sensitization defined approaches across programs of agency interest).

- Develop federated quality assurance networks providing Organisation for Economic Co-operation and Development (OECD) Good In Vitro Method Practices (GIVIMP)[26]

verification and proficiency testing for small labs—lowering barriers to entry while maintaining rigor.

(viii) How can the Federal government leverage and prepare for advances in AI systems that may transform scientific research—including automated hypothesis generation, experimental design, literature synthesis, and autonomous experimentation? What infrastructure investments, organizational models, and workforce development strategies are needed to realize these capabilities while maintaining scientific rigor and research integrity?

- **Invest in infrastructure to make use of existing data and strengthen data sharing.** Agencies have decades of toxicology data that are invaluable to developing predictive databases. Improved databases are critical for organizing existing data, enabling retrospective analyses, and supporting read-across approaches.
- Invest in infrastructure to expand Environmental Progection Agency and NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) computational tools (e.g., Integrated Chemical Environment (ICE)),[27] Open (Quantitative) Structure-activity/property Relationship App (OPERA),[28] Web App for Using Defined Approaches to Predict Skin Sensitization Hazard and Potency (DASS)[29]) and provide training for academic and Small and Medium-sized Enterprises (SME) users.
- **Clarify regulatory pathways for computational toxicology.** The Interagency Coordinating Committee on the Validation of Alternative Methods' (ICCVAM's) Biennial Progress Report highlights numerous computational tools.[30] Agencies should clarify pathways for regulatory consideration and acceptance of data from such tools.

(ix) What specific Federal statutes, regulations, or policies create unnecessary barriers to scientific research or the deployment of research outcomes? Please describe the barrier, its impact on scientific progress, and potential remedies that would preserve legitimate policy objectives while enabling innovation.

<u>The Animal Welfare Act and Animal Welfare Regulations</u>

The Animal Welfare Act (AWA; 7 U.S.C. §§ 2131–2156) and implementing regulations (AWR; 9 CFR Part 2) exclude "mice of the genus Mus, bred for use in research, (2) horses not used for research purposes, and (3) other farm animals, such as, but not limited to livestock or poultry, used or intended for use as food or fiber, or livestock or poultry used or intended for use for improving animal nutrition, breeding, management, or production efficiency, or for improving the quality of food or fiber,"[31] species that constitute the vast majority of animals used in experimentation and testing.

The exclusion of the majority of animals used for the activities the AWA and AWR are mandated to regulate undercuts consistency in minimum welfare standards and comprehensive reporting

across federally funded research, obstructing any attempts to measure the reduction of animal use that has been promised by certain agencies. The inability to measure progress toward these agencies' goals is a barrier to achieving their mission: to make biomedical research and regulatory testing more human-relevant, and thus advance science that better serves human health and the environment.

The Interagency Coordinating Committee on the Validation of Alternative Methods' (ICCVAM) Roadmap notes that measuring non-animal method implementation impact is difficult due to limited ability to quantify animals used for toxicity testing.[32] The Government Accountability Office's (GAO) 2019 *Animal Use in Research* report recommended that agencies propose metrics to help them better monitor progress in reducing animal use and to report their progress to the public.[33] Agencies should build on this report by developing strategies to compile quantitative information on their use and acceptance of non-animal testing approaches relative to tests on animals. At a minimum, each agency can report the number of *in vitro* and *in vivo* toxicity tests conducted internally or commissioned by the agency and their endpoint/purpose and the number submitted by companies to meet agency requirements or recommendations. Where applicable, this number can also include the number of tests waived based on scientific justification. To create an empirical foundation for evaluating the impact of new method adoption, to guide grant allocation toward methods that improve reproducibility, reduce costs, and align with reducing and replacing the use of animals, and to improve their ability to prioritize activities, agencies should track animal use by categories, e.g., endpoint and purpose. This is a practicable next step that has been shown to be feasible in the collection of statistics within the European Union and the United Kingdom.

The AWA and AWR also don't mandate the use of non-animal methods when possible, only the considerations of alternatives to painful or distressing procedures, which could still involve animal use, and the perfunctory assurance that the experimenter has searched the literature for relevant alternatives (and which is poorly enforced[34]).

The absence of a directive to use non-animal methods whenever possible acts as a barrier to the uptake and further development of these methods which are more predictive and better aligned to societal ethics. Under the current regulations, researchers are incentivized to ask, "Can I justify animal use?" rather than "Can I avoid animal use?" This promotes stagnation rather than innovation, where scientifically superior non-animal methods may be avoided because the regulatory framework does not actively reward or protect their use.

To correct these barriers to scientific progress, the AWA and AWR should be amended in the following ways:

- Inclusion of all species used in biomedical research and regulatory testing and purpose of use, so that reduction of their use and success in the implementation of non-animal methods can be tracked.
- Addition of measures to ensure a thorough search of non-animal methods available to answer the research question has been conducted before animal use is approved

The Public Health Service Policy on Humane Care and Use of Laboratory Animals

The Health Research Extension Act of 1985 requires that NIH-funded institutions comply with federal policies and guidelines in their treatment of vertebrate animals in laboratories and creates the legislative mandate for the Public Health Service Policy on Humane Care and Use of Laboratory Animals (PHS Policy). NIH's Office of Laboratory Animal Welfare (OLAW) implements and interprets the PHS Policy, as well as evaluates institutions' compliance with it.

Like the AWA, neither the PHS Policy nor its standards document, *The Guide for the Care and Use of Laboratory Animals* (*The Guide*), require the numbers of animals used in applicable research projects to be counted. The result is that total numbers of animals used in U.S. laboratories are only estimates, in contrast with the clear statistics on animal use required in Canada, the United Kingdom, and the entirety of the European Union. As explained above, this opacity is a barrier to advancing biomedical research and regulatory testing to better protect human health and the environment.

Regarding the prioritization of non-animal methods, *The Guide* is only slightly more progressive than the AWA/AWR, stating that it endorses "consideration of alternatives (in vitro systems, computer simulations, and/or mathematical models) to reduce or replace the use of animals" and that experimenters and Institutional Animal Care and Use Committees (IACUCs) should consider the "availability or appropriateness of the use of less invasive procedures, other species, isolated organ preparation, cell or tissue culture, or computer simulation."[35] But these statements are not operationalized; experimenters are compelled only to *consider* alternatives and are not required to use non-animal methods when suitable ones exist, or even when they would provide more valuable results.

Together in their current form, the AWA/AWR and PHS Policy/*The Guide* only regulate *how* animals are used, not *whether* animals should be used when non-animal methods are scientifically sufficient or superior, and these limitations are a barrier to scientific progress.

PHS Policy should be amended in the following ways:

- Mandated counting of all animals of all species used in biomedical research and regulatory testing, so that reduction of their use can be tracked
- Requirement of a documented non-animal methods assessment before animal use can be approved by an IACUC

Other barriers to scientific research and application and recommendations for improvement

- **The Code of Federal Regulations (CFR) codifies outdated testing approaches.** The adoption of 21st-century testing approaches has been slowed by the retention of outdated data requirements codified in the CFR, e.g., in Title 40 CFR Part 158 "Data Requirements for Pesticides."

- **The acceptance status for specific test methods is often unclear.** For example, the FDA's Center for Devices and Radiological Health accepts human skin patch test results under certain conditions, but not all reviewers are aware. There is a need for clarity and transparency within and across agencies.

- **Hazard category cut offs can be arbitrary.** Review arbitrary animal test hazard category thresholds to identify opportunities to reduce animal use without compromising health protection. For example, in some cases, such as acute systemic toxicity testing, certain EPA Office of Pesticide Programs' hazard categories can be combined without affecting the protection of human health.

- **Hazard categories are not harmonized.** Encourage federal and state agencies to transition to the Globally Harmonized System (GHS); new Organisation for Economic Co-operation and Development (OECD) *in vitro* test guidelines are aligned to GHS categories. This step would expedite the adoption of modern methods.

- **Validation processes are outdated.** Streamline processes to gain confidence in new approaches that demonstrate technical reliability, biological relevance, and fitness for purpose. Traditional interlaboratory ring trials can be lengthy and expensive; instead, validation should focus on whether new approaches fulfill intended purposes and provide technically reliable, human relevant information. The Interagency Coordinating Committee on the Validation of Alternative Methods' (ICCVAM's) 2024 report *Validation, Qualification, and Regulatory Acceptance of New Approach Methodologies* emphasizes biological relevance over direct animal comparators and acknowledges that new approaches may provide better quality, more relevant information for regulatory decisions.[36] Agencies should update validation strategies accordingly and never prospectively request animal data to validate a new method.

- **Coordination and recognition of international validation is lacking.** When a method undergoes extensive validation and gains acceptance by international standards bodies, agencies should not require re-validation. For example, OECD Test Guideline (TG) 439 (Reconstructed Human Epidermis—RhE—for skin irritation) was published in 2010 (updated 2021). In 2018, the TG was adapted for an International Organization for Standardization (ISO) sponsored interlaboratory validation of medical device extracts; 16 labs (including FDA) participated and concluded RhE tissues are a robust model for detecting irritant activity, even at low levels of strong irritants in device extracts. ISO subsequently published ISO 10993 23, preferring *in vitro* methods for medical devices. This standard is recognized by EU Member States, Australia, Japan, and China. The FDA should fast track acceptance.

- **A streamlined process to adopt international non-animal standards is lacking.** When non-animal methods are approved elsewhere (e.g., shellfish toxicity testing standards), establish a process for U.S. approval and implementation and a system to identify roadblocks if methods are not adopted domestically.

- **Barriers prevent modernizing over-the-counter monographs.** Substantial fees for Over-the-Counter Monograph Order Requests (OMORs) can deter replacement of outdated methods. The FDA should initiate timely monograph updates when warranted and create a free process for nominating updates. Fee waivers—similar to those for drug safety label updates—should be granted when updates modernize test methods, reduce/replace animal use, and improve public health protection.
- **A lack of transparency hinders internal agency alignment, reviewer consistency, and industry adoption of modern, human relevant tools.** For example, the Environmental Protection Agency Office of Pollution Prevention and Toxics' (OPPT's) made positive strides towards transparency via the publication of its eye irritation decision framework, which discourages the *in vivo* rabbit Draize test in favor of non-animal approaches assessing the full severity range.[37] Other agencies should follow the EPA's lead by issuing guidance supporting modern, non-animal methods, e.g., the FDA could immediately issue guidance for skin irritation (medical devices), shellfish biotoxin assessment, sunscreen safety, pyrogenicity, and anticaries testing—and withdraw obsolete guidance superseded by updated approaches.
- See also responses to:
    - *(i)* Other recommendations
        - Facilitate agency procurement of validated non-animal platforms for intramural research programs so that federal purchasing power can boost industries developing these technologies, create early markets, and encourage private investment.
    - *(ii)* Suggested amendments to the Bayh-Dole Act

(x) How can Federal programs better identify and develop scientific talent across the country, particularly leveraging digital tools and distributed research models to engage researchers outside traditional academic centers?

- Deliver Organisation for Economic Co-operation and Development (OECD) Good In Vitro Method Practice (GIVIMP)[38] training and certification online.
- Host open challenges and hackathons to develop, characterize, and adopt new approach methods and strategies.
- Offer internships at the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) to build capacity and familiarity with non-animal methods.

(xi) How can the Federal government foster closer collaboration among scientists, engineers, and skilled technical workers, and better integrate training pathways, recognizing that breakthrough research often requires deep collaboration between theoretical and applied expertise?

Transition grants to foster collaboration and innovation

Many federally funded researchers received their formative training in animal-based methods, despite the well-known problems with translation and replicability of animal experimentation, and lack exposure to human-relevant, non-animal technologies. Transitioning to these approaches is challenging because it requires retraining costs (specialized courses, certifications), slow productivity periods while researchers learn new techniques, purchasing new equipment, and access to interdisciplinary expertise (bioengineering, computational modeling) that animal-focused laboratories often lack.

Transition grants, which would be used to retrain animal experimenters to be proficient in non-animal technologies, could create structured opportunities for biologists to work alongside engineers and computational experts, integrating theoretical and applied expertise in real-world projects, and foster collaboration that would benefit all fields. By retraining today's researchers, the federal government can ensure the next generation of scientists is fluent in cutting-edge, human-relevant methods, positioning the U.S. as a global leader in biomedical innovation.

Federal agencies that fund biomedical research should establish a program to disseminate these transition grants, which should cover training expenses, provide bridge funding to offset temporary productivity declines during training periods, support equipment acquisition and shared-use access for non-animal technologies, and offer incentives to the bioengineers, data scientists, and skilled technicians that will be necessary to assist with this training.

Create free, federally supported training programs in non-animal methods

Transitioning to modern, non-animal approaches requires specialized knowledge in bioengineering and computational modeling, but training opportunities are limited, expensive, and often inaccessible to smaller institutions or early-career scientists. This creates silos between theoretical biologists and applied engineers, slowing innovation and perpetuating reliance on animal experiments.

The federal government can solve this problem by developing free online and in-person training modules on non-animal methods and offer certifications that can then be recognized in NIH grant applications. The programs should also provide travel and stipend support for trainees from rural research centers. By making non-animal methods training free, accessible, and collaborative, the federal government can dismantle silos between disciplines, reduce reliance on animal models, and ensure U.S. researchers remain globally competitive in advanced biotech and AI-driven health solutions.

The following offer examples on which these training programs could be based:

- The Physicians Committee for Responsible Medicine runs an award-winning Summer Immersion on Innovative Approaches in Science[39] geared to connect undergraduate and graduate students, post-docs and early-career scientists with government, industry, and academic non-animal methods experts through scientific talks, career development workshops, poster presentations, technology demonstrations, case studies, networking opportunities, and more. The event is free to attend.

- The European Commission's Joint Research Centre hosts an annual Summer School on Non-Animal Approaches in Science[40] where students and early career researchers are educated on complex *in vitro* methods and computational modelling used in biomedical research and regulatory applications.

- The Dutch Transition Programme for Innovation (TPI) runs "helpathons," lively workshops during which an animal experimenter brings a specific question—how they can answer their research question using non-animal methods instead of animals—to a community of diverse participants who engage in creative collaborate to solve the puzzle. TPI also hosts a virtual marketplace where professionals from all sectors can connect and exchange information, knowledge, or data to accelerate animal-free innovations.[41]

Other recommendations

- **Require agencies to be actively involved in in-person and virtual training and informational events.** For example, the EPA Office of Pesticide Programs convenes in-house training on the use of *in vitro* and *in silico* methods for toxicity assessments and maintains a catalog of training materials on different approaches. The agency also participates in webinars and conferences on the development and use of non-animal methods, helping to foster collaboration among numerous stakeholders.

- **Mandate regular training for agency staff on new methods and policies to ensure consistent feedback to industry and reduce delays.** Establish dedicated offices focused on developing, validating, and providing training on new approach methods (e.g., the Office of Research Innovation, Validation, and Application (ORIVA)).

- **Support hands-on courses** such as the Institute for In Vitro Sciences' program (https://iivs.org/education-outreach/practical-methods-for-in-vitro-toxicology-workshop/), which has proven fundamental for scientists and regulators adopting non-animal approaches. Managers should prioritize time for staff to attend.

- **Promote collaborative publications and public-private partnerships**, e.g., *Human-Relevant Approaches to Assess Eye Corrosion/Irritation Potential of Agrochemical Formulations*,[42] coauthored by the EPA, the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), European Commission Joint Research Centre, an NGO, and a not-for-profit testing organization; and Interagency Coordinating Committee on the Validation of Alternative Methods' (ICCVAM's) April 2018 workshop on Predictive Models for Acute Oral

Systemic Toxicity.[43] The latter was truly a public-private partnership that started with the curation of existing rat acute oral toxicity data by NICEATM and the EPA National Center for Computational Toxicology, followed by a global call for *in silico* models using the data. Subsequently, the toxicity predictions generated by the models will be made available via the EPA's Chemistry Dashboard, and there is ongoing discussion about using the models in a regulatory context.

- **Establish stakeholder forums** modeled on EPA's Acute Toxicity Alternatives Stakeholder Group[44] to provide regular updates, feedback mechanisms, and workgroups. In collaboration with its stakeholders, the EPA has set out a number of goals for adopting alternatives to acute toxicity testing and is giving regular updates to the stakeholder group. The forum also provides a feedback mechanism for industry and NGOs to provide comments, give advice, and participate in workgroups that deal with specific issues.

Encourage early company-regulator dialogue on testing plans and potential non-animal methods; where *in vivo* testing is required, consider parallel non-animal testing to build validation data and operational familiarity. For example, the recent workshop report, *Alternatives to HIST for acellular pertussis vaccines: progress and challenges in replacement*, encourages applicants to engage reviewers prior to the submission of data from alternative methods.[45] Companies and reviewers can gain from constructive dialogue on the potential use of non-animal test methods in specific applications prior to conducting testing.

(xii) What policy mechanisms would ensure that the benefits of federally-funded research—including access to resulting technologies, economic opportunities, and improved quality of life—reach all Americans?

<u>Stop funding experiments on animals conducted in foreign countries</u>

Between 2011 and 2021, foreign facilities received $2.2 billion in taxpayer funds from NIH for experiments on animals to be conducted in overseas laboratories, where the U.S. has no oversight. This funding was awarded for 1,177 grants and 180 contracts to 200 foreign organizations in 45 countries. NIH has zero oversight regarding how these organizations operate or how the money is spent. Roughly 90% of the foreign organizations that received NIH funding in the last five years are exempt from its audits. Moreover, for fiscal years 2019 and 2020, NIH never received 74% of the audits it required from foreign laboratories it funded and didn't follow up on the missing audit reports with the facilities receiving these funds. The agency doesn't inspect foreign laboratories or arrange third-party inspections to ensure that the facilities meet basic animal welfare standards and issues funds without verifying that claims in grant applications and progress reports are true.

A recent example can be made by NIH's two decades of funding of the Caucaseco Scientific Research Center in Colombia. A PETA exposé[46] revealed horrific animal abuse and research misconduct that resulted in the closing of the center, the rescue of nearly 300 monkeys and mice,

the ineligibility of the center to receive future NIH grants, and a more than $281,000 fine by a regional environmental agency. The facility, which received more than $17 million from NIH, had used unsupported information on NIH grant applications regarding what their center really did and how it operated, violated animal care and use guidelines, ignored local animal welfare regulations, kept monkeys in filthy conditions, and allegedly mishandled human samples and manipulated data. Another example is the renowned Karolinska Institute in Sweden, which has received NIH funding since 2004 to conduct experiments on rabbits and has failed to meet basic standards of animal welfare.[47]

Federally funded research is intended to serve the public interest by advancing U.S. scientific leadership, generating domestic economic opportunities, and improving health outcomes for Americans. When NIH funds animal experiments conducted outside of U.S. regulatory, ethical, and scientific oversight, those public benefits cannot be guaranteed. Robust oversight is a prerequisite for ensuring that publicly funded research yields trustworthy, high-quality results that can be translated into meaningful health advances for all Americans. When NIH lacks the ability to inspect facilities or enforce even its minimal standards, the resulting research cannot reliably serve as the foundation for treatments, diagnostics, or public health interventions intended for American patients.

Also, when the data generated in foreign laboratories fails to translate into clinically relevant technologies, it cannot contribute to the U.S. biomedical workforce nor strengthen domestic research infrastructure or innovation ecosystems, as demonstrated in the Caucaseco case described above.

A bipartisan bill, the Cease Animal Research Grants Overseas (CARGO) Act (HR 1085, S 1802), was introduced by Reps. Troy Nehls (R-Texas-22) and Dina Titus (D-Nev.-01), and Sens. Rick Scott (R-Fla.) and Cory Booker (D-N.J.) to address the many issues resulting from NIH's funding of experiments on animals in foreign laboratories. The landmark bill would prevent NIH from funding any experiments on animals outside the U.S., stopping the flow of taxpayer money to organizations over which the U.S. has no oversight. By ensuring that NIH funds are spent within the U.S., the CARGO Act would realign federal research investment with its intended beneficiary (the American public) and help ensure that discoveries made with taxpayer dollars translate into medical advancements, improved public health, and economic growth within the communities that support this research through their taxes. The CARGO Act has been endorsed by more than 100 national, state, and local groups concerned about animals, effective science, human health, and responsible public policy.

Harness non-animal methods to serve all Americans

Experiments on animals have historically dominated biomedical research that is funded by the tax dollars of all Americans; yet they are fundamentally incapable of capturing the biology of those same citizens. This is one area where non-animal methods excel, as they can be built upon and tailored to cells and data from any single, unique individual, enabling precision medicine for all Americans. Non-animal methods provide the opportunity to address human population

variability and susceptibility that tests on animals cannot. *In vitro* assays and microphysiological systems can be developed to represent specific populations to assess human health susceptibility and outcomes, and *in silico* models allow more comprehensive clinical trials to be conducted.

The federal government should mandate that non-animal method-generated datasets, such as organoid response profiles, and computational toxicology models, be deposited in FAIR-compliant public repositories and ensure these resources are accessible to community hospitals, rural institutions, and small biotech firms to expand American innovation beyond elite, mostly urban research centers.

Conclusions

If acted upon, the above recommendations will accelerate the American scientific enterprise, enable groundbreaking discoveries, hold federal agencies accountable, promote transparency, align with public morals, spare millions of animals, reduce healthcare costs, and ensure that scientific progress and technological innovation benefit all Americans.

PETA scientists have a proven track record of productively assisting many Fortune 100 corporations as well as regulatory and government agencies. This assistance includes providing expert opinions, regulatory advice, and technical support in a broad range of fields. We are available for consultation on these and any other matters related to the use of animals in research and testing.

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