Science Advancement & Outreach
A DIVISION OF PETA

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Request for Information: Accelerating Innovation through ARPA-H and FDA Collaboration

Response from People for the Ethical Treatment of Animals

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In order to accelerate "better health outcomes for everyone," ARPA-H and the FDA must work together to transition to robust non-animal testing strategies for safety and efficacy testing. Numerous scientific studies and reviews have demonstrated that an alarming number of animal tests fail to translate to humans.

The National Institutes of Health reports that **95 percent of novel drugs[1]—which have practically all gone through animal testing—fail in human clinical trials**. These failures feed into the enormous cost (>$2 billion per drug) and lengthy timeline (10-15 years) for bringing a new drug to market. Drug failure statistics are even more dire in certain disease areas (stroke,[2] sepsis,[3] Alzheimer's disease,[4] cancer,[5] and HIV vaccines,[6] for example), but the problem is largely disease agnostic.

The failure of preclinical animal tests to predict safety and efficacy in humans not only delays new treatments from getting to the clinic, drives up the costs of medications, and misuses funds, but can also directly lead to loss of life. Here are a few examples:

- In 2016, a Portuguese company developed a drug intended to help with mood, anxiety, and motor problems related to neurodegenerative disease. The six volunteers who participated in their phase I clinical trial experienced such adverse reactions after oral administration of this drug that they had to be hospitalized. One participant died.[7] These effects were not predicted by preclinical tests in animals, despite the fact that animals were given doses 400 times stronger than those given to the human volunteers.
- Preclinical animal tests also failed to predict the tragic outcome of the 2006 clinical trial for Theralizumab, an immunomodulatory drug, in which six human volunteers were given a dose 500 times smaller than that found safe in animal studies, but ended up facing life-threatening conditions involving multi-organ failure.[8]
- In the phase II study of fialuridine, an antiviral drug being tested against hepatitis B, almost half of the 15 patients experienced severe toxicity, which included liver failure, lactic acidosis, and pancreatitis, and resulted in the death of five of the patients.[9] Two additional patients required emergency liver transplants to survive.

This toxicity was not predicted by preclinical tests performed on dogs or monkeys and was not well replicated in post-trial studies in rats, who were administered a dosage that was 1000 times greater than what was given to humans.[10]

One study showed that animal tests fail to detect potential side effects of drugs in humans 81 percent of the time.[11] It is unfair to continue to burden U.S. taxpayers with the costs of ineffective research models and the subsequent elevated cost of drug development, all while putting their health at risk.

Advanced technologies that recapitulate human biology are increasingly shown to be more accurate at reflecting human outcomes when compared to animal tests. Here are a few examples:

- A human blood vessel-on-a-chip was able to predict human thrombosis caused by an antibody therapy.[12] This therapy had previously been determined to be safe following preclinical animal tests, but clinical trials had to be stopped after humans given the drug developed blood clots, which were not predicted by the experiments on animals.
- A computer algorithm was able to predict the human toxicity of new chemicals for nine hazard determinations with greater accuracy than animal tests.[13]
- *In vitro* tests using human cells predicted human liver injury caused by the diabetes drug troglitazone, which had not been detected in animal tests.[14] Troglitazone had been withdrawn from the market due to severe and fatal liver toxicity that killed at least 63 people.
- A human liver-on-a-chip was able to correctly identify 87% of drugs that passed animal testing but caused drug-induced liver injury in patients.[15] These drugs had caused nearly 250 human deaths and 10 liver transplants. Drug-induced liver injury is estimated to kill 7.6% of people who experience it.[16]

Reliance on animal models is diverting resources away from more promising research and development methods, delaying discoveries, increasing drug costs, compromising the testing of effective drugs and treatments, and limiting our ability to protect human health.

Critically, the recent passage of the FDA Modernization Act 2.0 has signaled that the public, the scientific community, and policymakers want to modernize the way biomedical research and testing are conducted, with greater focus on the importance of human-relevant methods and greater awareness of both the ethical and scientific issues that surround animal experimentation. The potential for this groundbreaking legislation to benefit animals and humans alike is why more than **200 organizations**—including biotech companies, medical associations, animal advocacy organizations, patient advocacy groups, and pharmaceutical companies—supported the bill.[17]

To this end, we recommend that ARPA-H and the FDA work together to do the following:

1. **Prohibit funding of animal use for drug discovery and preclinical testing in areas where it has been demonstrated that the animal tests and paradigms poorly predict human outcomes.** Replace animal use with more predictive non-animal systems based in human biology and prioritize validating these non-animal tests for regulatory acceptance. ARPA-H should implement a policy to fund promising human-relevant research methods, such as organs-on-chips, sophisticated uses of human stem cells, -omics technologies, imaging, and computer modeling instead of animal tests. A policy to fund these methods, which recapitulate human physiology and biology without using animals or their tissues, will benefit U.S. biomedical research as a whole, increase the safety of drugs approved by the FDA, and reduce the current length of time and failure rate associated with human drug development.
2. **Conduct systematic reviews on the predictive ability of animal use in drug discovery and preclinical testing to identify additional areas in which non-animal methods are available, could be available if provided increased resources, and/or where the use of animals has failed to protect human health.** In the latter case, animal studies must simply be stopped in order to prevent future adverse outcomes. ARPA-H could announce contracts to fund researchers to complete these systematic reviews, which would be then used by the FDA to make evidence-based decisions about regulatory acceptance.
3. **Work with other world leaders to harmonize and promote international acceptance of non-animal testing methods for regulatory toxicity testing requirements.** The regulatory acceptance of non-animal techniques in one region or country is an open door to international modernization of testing requirements. Likewise, a lack of international acceptance is a barrier to the use of a non-animal method. Therefore, we advocate that the FDA liaise with industry, research agencies, and relevant nongovernmental organizations worldwide to establish and promote clear paths to the validation and harmonization of non-animal techniques for regulatory testing requirements.

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