Support the FDA Modernization Act to Lift the Animal-Testing Mandate for Drug Development Protocols Overseen by the FDA

The FDA Modernization Act, H.R. 2565 and S. 2952, would amend the Federal Food, Drug and Cosmetics Act (FFDCA) to revamp regulatory standards to allow for more modern and effective nonclinical test methods. These changes will provide safer drugs, quicker delivery of life-enhancing drugs, and decrease costs for drug developers and patients. This legislation will allow for the more rapid development of human-based biological systems and foster the acceptance of superior testing methods, widely known as New Approach Methodologies (NAM). These bills do not ban animal testing but allow the government and industry to deploy the best and most predictive test methods in drug development protocols where scientifically suitable.

In follow-up questions during his nomination process, FDA Commissioner Robert Califf said the follow about nonanimal test methods:

> We are entering a new era of systems biology with computational methods that enable a more efficient pre-clinical and clinical development and evaluation approach to drug and device development. I support the shift toward the use of non-animal methods where scientifically supported, and if confirmed would work to ensure the Agency continues its strong commitment to supporting the 3Rs: to replace, reduce, and refine the use of animals in studies. This effort must be done carefully to ensure that the system continues to protect human subjects during drug and device development and patients when products are marketed.[1]

The Problem

Can the Current Drug Development System with a 90 to 95% Failure Rate Bring the Required Treatments and Vaccines for Americans?

- **High Drug Prices, Slow Approvals, Serious Side Effects:** American consumers face several dilemmas when it comes to the drugs they need: extraordinarily high costs for drugs, inordinately long wait periods in bringing the drugs to market, and, even after the drugs are approved for common use, serious health side effects for consumers often result from taking the drugs.

- **Onerous Regulations and High Failure Rates for Drug Sponsors:** The pharmaceutical industry is burdened by outdated FDA statutes and regulations that bar the use of faster, cheaper, more reliable test methods. This regulatory framework burdens business and exposes the public to unacceptable risk and harm, and delays or entirely stifles the movement of life-saving drugs into the marketplace.

- **Outdated, Unproven Test Methods Discourage Rigorous Science:** Significant investments in technology development and research have resulted in transformative scientific breakthroughs. These testing strategies are often not put into practical use because of FDA requirements to use animal testing strategies even when it's clear they produce inferior results, apart from their higher cost and longer time frame for completion.

The Solution

The FFDCA must be updated to broaden options for drug developers for nonclinical testing to include modern, innovative, human-relevant test methods. These modifications will allow drug sponsors to apply state-of-the-art tools to predict how humans will respond to their drugs in clinical trials, thereby reducing attrition, shortening time to market, saving millions of dollars, and providing safer and more effective drugs for American consumers.

Under language of H.B. 2565 and S. 2952, traditional testing would still be required in the absence of a scientifically recognized modern test method. Where a scientifically recognized modern test method exists or a particular purpose, sponsors would have the option to use the test method in consultation with FDA.

Background

1. The Current Regulatory Scheme is Bad for Public Health

The Federal Food Drug and Cosmetics Act (FFDCA) 21 USC § 355 requires drug sponsors to submit data from nonclinical testing before investigational drugs are used in human trials. The statute mandates traditional animal data even though much of the required safety and efficacy data can be obtained from modern methods that are more predictive of human outcomes. The acceptance of alternate methods can, in many instances, produce better human health outcomes and quicker approvals. As a matter of moral concern for patients and for animals and out of a concern for cost and efficiency, FDA should revamp its requirements to allow for better, faster, safer testing methods and not require outdated ones. These bills would not eliminate animal testing, but to allow for superior alternatives where suitable.

- Adverse reactions to drugs, taken as prescribed, is the 4th leading cause of death in the United States. Adverse events from *properly* prescribed drugs cause 1.9 million hospitalizations per year, and 128,000 of these are fatal.[2]
- A major contributing factor to adverse drug reactions (ADRs) is the inadequacy of nonclinical animal tests: one recent study showed that 63% of ADRs had no counterpart in animals, and less than 20% had a positive corollary in animals.[3]
- Including non-animal test methods will make nonclinical testing more efficient and accurate in predicting human health outcomes, getting safer, more effective drugs into the marketplace sooner to help people with health challenges or crises.
- Better testing methods will minimize the exposure of clinical trial participants and patients to serious adverse events and death during human clinical trials and beyond.
- The current system stifles research and testing into a wide range of health conditions because the companies make a judgment that they cannot make profits from drugs with

limited market potential. Companies must invest in drugs with high market potential because they must make high-risk, 10-year, billion-dollar investments in research to bring a single drug to market. This corporate screening process leaves health concerns experienced by a smaller subset of the public to do without life-saving treatments.

2. The Current Regulatory Scheme is Bad for Industry.

FDA regulations and the FFDCA require drug developers to rely on traditional animal tests that place immense and unnecessary financial and regulatory burdens on companies for no good reason. This results in delays in the approval process, costing millions of dollars. It typically takes 10 years to bring a new drug to market with an average cost between $1 billion and $6 billion.[4],[5]

- Use of modern test methods would improve results and lower attrition rates. Between 90 and 95% of drugs found safe in nonclinical tests fail during human clinical trials due to toxicities not predicted by traditional animal tests or because of lack of efficacy.[6]
- Failing 90 to 95% of the time after spending millions or billions of dollars imposes extraordinarily onerous burdens on companies and then those costs are passed on to consumers in the form of higher drug prices, marring the public perceptions of companies. Yet, drug sponsors have no choice but to follow these archaic regulations.
- To lower drug costs, restrictive regulations must be changed to give drug sponsors the ability to innovate and get better drugs approved years earlier and at less cost for companies and consumers.

3. **The Current Regulatory Scheme Stifles Innovation and is Bad Science.**

Amending FFDCA and making regulatory changes will accelerate innovation and get safer, more effective drugs to market more quickly.

- In addition to falsely identifying a toxic drug as "safe," animal tests can falsely label a potentially useful therapeutic agent as toxic. Thus, of the many thousands of drugs that have failed in animal tests, some might have worked in humans.
- A recent Phase 2b human clinical trial of Johnson & Johnson's HIV/AIDS vaccine failed because of lack of efficacy. Animal data had shown 90% efficacy.[7] This is consistent with the 30+ year effort to develop a HIV/AIDS vaccine. The animal data show promise, but the vaccines do not work in humans.
- On September 2, 2021, FDA's Cellular, Tissue, and Gene Therapies Advisory Committee said animal models are "problematic" in assessing the safety risks of gene therapies derived from adeno-associated virus (AAV) vectors. There have been "severe" adverse events in AAV vector clinical trials, including instances of acute liver and kidney failure in children. One third of the 500 children under the age of 2 treated with Zolgensma had at least once adverse event of hepatoxicity.[8]
- Studies show that while toxicity in animals may also be present in humans these tests are not consistent or reliable and provide nearly no insight into the possibility or likelihood of toxicity or the absence of toxicity in humans.[9]
- In one protocol, researchers studied six drugs to determine which of the 78 adverse effects that occurred in humans would occur in dogs or rats. Effects that are undetectable in

animals (e.g., headaches) were not taken into account. Less than half (46%) of the remaining side effects were detected in the animals - slightly less than the expected results from flipping a coin. In other words, animal tests were wrong 54% of the time.[10]

- Another study of drug registration files was conducted to determine whether post-marketing serious adverse reactions to small molecule drugs could have been detected on the basis of animal data. Of 93 serious adverse reactions related to 43 small molecule drugs, only 19% were identified in animal studies as a true positive outcome.[11]
- Vioxx appeared safe and even beneficial to the heart in animal tests but was withdrawn from the global market in 2004 after causing an estimated 320,000 heart attacks, strokes, and cases of heart failure worldwide – 140,000 of them fatal.[12] Nine of 11 studies on mice and rats had shown Vioxx or other COX-2 inhibitors to be safe for animal hearts and blood vessels. In fact, six different animal studies—in four different species—showed Vioxx was actually protective against heart attacks and vascular disease.[13] Litigation related to these adverse reactions has cost billions to the manufacturer.
- There have been at least 200 treatment-related (non-disease progression) deaths in human clinical trials the US in the last six years.[14]
- Many biologics recognize only human targets, and biologics make up 40 percent of the drug development pipeline.[15] Animal studies are not possible because the molecular target of the therapeutic (e.g., monoclonal antibody, crRNA) is human-specific and there is no cross reactivity with animal targets.
- The use of nonhuman primates for drug and vaccine development is fraught with ethical concerns as well as animal shortages. Additionally, immune responses to infectious diseases and vaccines are known to be species-specific. To rapidly respond to emerging pandemics, human-based testing systems that can replicate human immune responses are necessary.
- Medicine is changing rapidly as we move into the age of personalized/precision medicine. Here animal models will have no real value since other species will not capture biological variation among humans. Nonclinical tests or studies using human cells and tissues can portray biological variation among the human population. They have the potential to serve as "clinical trials in a lab" and to test a drug's safety and effectiveness for individual patients. This is the near future of biomedical science, and animal testing has little of value for this new paradigm.
- Human-relevant cell-based assays, organs-on-a-chip, human-on-a-chip models, and sophisticated computer modeling have been developed to predict human response more accurately to new drugs, yet FDA does not officially acknowledge these superior models in their regulations, requiring drug sponsors to use inferior animal models.
- Market growth for non-animal tests is outpacing traditional animal tests, but FDA has yet to embrace the new technology in their regulations. The global market for laboratory animal models is predicted to grow at a compound annual growth rate (CAGR) of 5.6% for the period of 2018 to 2023. For the same period, cell-based assays are predicted to grow at a compound annual growth rate (CAGR) of 10.2%, and organ-on-a-chip assays should grow at a compound annual growth rate (CAGR) of 39.9%.[16]
- Updates to the FFDCA would provide drug sponsors more options for testing the safety and efficacy of drugs to improve clinical trial attrition rates, cut time to market in half, and substantially reduce R & D costs which could cut drug prices fivefold.[17]

4. Nonanimal Test Methods Are Becoming More Sophisticated

A) Organs on Chips and Computer Modeling

- In a recent study, researchers assessed the performance of 780 human Liver-Chips across a set of 27 known hepatotoxic and non-toxic drugs. *Importantly, the study demonstrated that the Emulate Liver-Chip was able to correctly identify 87 percent of the tested drugs that caused drug-induced liver injury in patients despite passing through animal testing.* At the same time, the Liver-Chip did not falsely flag any drugs as toxic, supporting its use in toxicology screening workflows.
- The biotech company Quris uses Artificial Intelligence-powered miniaturized "patients-on-a-chip" to avoid the tremendous risks and costs of failed clinical trials and eliminate the reliance on ineffective animal testing.

B) Disease-Specific Models

- Cystic Fibrosis — Microfluidic organ-on-a-chip preclinical models of the cystic fibrosis lung airway could help bring new and much-needed drugs, and personalized medicine approaches to patients. Studies using organs-on-a-chip models have been funded by the Cystic Fibrosis Foundation.
- ALS — Lab on a chip can make a major contribution as a biomimetic micro-physiological system in the treatment of neurodegenerative disorders such as ALS.
- Alzheimer's Disease — Preclinical stages of Alzheimer's disease (AD) and mild cognitive impairment have been modeled with a Human-On-A-Chip SYSTEM. To date, more than 100 potential therapeutics in development for AD have been abandoned or failed during clinical trials. These therapeutics relied on research conducted in preclinical animal studies, which often are unable to accurately capture the full spectrum of the human disease.
- Parkinson's Disease — Scientists have designed an "organ-on-a-chip" device that can grow the brain cells most affected in people with Parkinson's Disease. The Michael J. Fox Foundation has funded studies using organs on chips using the Lung-Chip device, to determine exactly how safe are specific Parkinson's drugs and to try to understand why they have a negative effect on the lungs.

C) Cancer

- Organ-on-a-Chip technology allows researchers to recreate the human tumor microenvironment in vitro, enabling mechanistic studies of cancer cell behavior and drug efficacy and safety.
- Organ-Chips and Omics Advance Cancer Research — groundbreaking research is being performed as a Cancer Grand Challenges research project, namely, STrOmal ReprograMming Cancer — or STORMing Cancer.

D) SARS-CoV-2

- The Biomedical Advanced Research and Development Authority (BARDA) awarded Harvard's Wyss Institute funding to develop to study vaccine responses. "The ongoing COVID-19 pandemic has made clear the need for rapid vaccine development, and this can be hampered by the lack of animal models that faithfully replicate human vaccination responses," said Donald E. Ingber, M.D., Ph.D., Founding Director of the Wyss Institute for Biologically Inspired Engineering at Harvard University.
- The Chemical Biological Center at the U.S. Army Combat Capabilities Development Command (CCDC) is working to better understand how COVID-19 attacks lung cells

using the Emulate Alveolus Lung-Chip that recreates human biological systems. "In the past, the closest researchers could get to something like this was by introducing a virus into animals and then dissecting them," according to Dan Angelini, Ph.D., a Center research biologist. "With this, there is no need for animals in performing toxicological research."

- A recent study coming out of Harvard Wyss shows innate immune responses against a repurposed drug for COVID-19 using a lung-on-a-chip. Studies performed on the drug at the Wyss Institute in a Human Lung Alveolus Chip demonstrated that azeliragon significantly blocks the production of inflammation-causing cytokines including IL-6, IL-8, and IP-10 as well as RANTES, a key proinflammatory cytokine produced by virus-infected lung cells, following viral infection.

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