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FDA Modernization Act 2.0: The Beginning of the End for Animal Testing in Drug Development

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FDA MODERNIZATION ACT 2.0: THE BEGINNING OF THE END FOR ANIMAL TESTING IN DRUG DEVELOPMENT

By
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Historical drug testing protocols utilized animal testing to determine whether drugs were safe and effective for use in humans. However, recognizing that testing drugs on other species is potentially dangerous for humans, troubled by failures, unnecessarily expensive, and time consuming, the FDA Modernization Act 2.0, passed in December 2022, removed animal testing as a requirement for new drug applications. While this was an important step forward, a notable failure of that Act is that it did not go far enough to end animal testing. Accordingly, this Article proposes an FDA Modernization Act 3.0.

The FDA Modernization Act 3.0 would ensure the highest level of human safety by making drug development human centered. This would be accomplished by embracing cutting-edge technologies, including cell-based assays, human organ chips, and computer modeling. As proposed, the FDA Modernization Act 3.0 would favor human-centered drug testing by prohibiting animal testing where appropriate alternatives exist and adding a reporting requirement to document researchers' efforts to utilize human-centered testing in lieu of animal testing

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I. INTRODUCTION

What happens when the testing protocols for new drugs are insufficient and those drugs go on to kill patients? In the United States, the answer is: continue to allow those same protocols to test more drugs.

While this may sound hyperbolic, it unfortunately is not. The Food and Drug Administration approves new drugs for human use only after testing protocols determine them to be safe and effective for patients.[1] Until very recently, animal[2] testing has provided the basis for those approvals. While animal testing has allowed remarkable drug advancements, extrapolations from safety in animals to safety in humans can be unreliable. To be sure, new drugs determined to be 'safe' after animal testing have injured and killed humans.

The rise and fall of the drug Thalidomide is emblematic of the potential consequences of relying on animal testing. In the 1950s, the drug Thalidomide was marketed as a sedative agent.[3] Shortly after, it became a drug of choice for morning sickness.[4] But, the drug caused disastrous phocomelia[5] in 20,000 to 30,000 infants before its manufacturer

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[1] Federal Food, Drug, and Cosmetic Act of 1938 § 505, 21 U.S.C. § 355(b)(1)(A)(i).

[2] Throughout this Article, the term "animal" refers to nonhuman animals.

[3] K. Ghoreishi, *Thalidomide*, 4 ENCYCLOPEDIA OF TOXICOLOGY 523, 523 (2024).

[4] *Id.*

[5] *Id.* (Phocomelia is a rare congenital deformity in which the hands or feet are attached close to the trunk, the limbs being very underdeveloped or absent); Donald D. Davis & Steven M. Kane, *Phocomelia*, NAT'L CENT. FOR BIOTECHNOLOGY INFO. (June 12, 2023), https://www.ncbi.nlm.nih.gov/books/NBK559212/ (accessed Jan. 26, 2024).

withdrew it from the market.[6] Thalidomide was 'successfully' tested on ten rat strains, eleven rabbit breeds, two dog breeds, three hamster strains, eight primate species, and various cats, armadillos, pigs, guinea pigs, and ferrets.[7] Later animal testing specifically on pregnant rats, mice, and rabbits showed no abnormalities in their offspring.[8] Despite animal testing showing that Thalidomide was safe, those tens of thousands of infants suffered permanent, debilitating deformities not predicted by that animal testing.[9]

Still, the discovery of new drugs is crucial to finding treatments for diseases that cannot yet be cured or managed.[10] Drug discovery holds the promise of ending human diseases, treating genetic disorders, and extending human life expectancy. Yet, drug testing protocols in the United States do not take advantage of the technological progress made in drug testing, and the current system reflects this by continuing to utilize unnecessarily expensive, time consuming, and unreliable animal testing procedures.[11]

Thankfully, the federal requirement that new drugs be tested on animals was removed in December 2022.[12] Under the FDA Modernization Act 2.0, animal testing is no longer required in new drug applications.[13] Now, researchers can base clinical trials on preclinical tests that utilize human physiology and can be run quickly and simultaneously, streamlining the process.[14]

However, a notable failing of the FDA Modernization Act 2.0 is that it does not go far enough to end animal-testing. As this Article will discuss, development of human drugs should be *human*-centered. Focusing on human-centered testing by utilizing alternatives to animal testing can hasten drug discovery, improve patient safety, enhance pharmaceutical industry productivity, and reduce costs.[15] An FDA Modernization

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6 Gail A. Van Norman, *Limitations of Animal Studies for Predicting Toxicity in Clinical Trials: Is it Time to Rethink Our Current Approach?,* 4(7) JACC: Basic to Translational Science 845, 846 (2019).

7 *Id.* at 846–847.

8 Joanna Yang & Chanapa Tantibanchachai, *Studies of Thalidomide's Effects on Rodent Embryos from 1962-2008*, EMBRYO PROJECT ENCYCLOPEDIA (Mar. 7, 2014), https://embryo.asu.edu/pages/studies-thalidomides-effects-rodent-embryos-1962-2008 (accessed Jan. 14, 2024).

9 Van Norman, *supra* note 6, at 846.

10 *See generally* Gregory Nierode et al., *Cell-Based Assay Design for High-Content Screening of Drug Candidates*, 26.2 J. MICROBIOLOGY BIOTECHNOLOGY 213, 213 (Feb. 2016) (discussing the importance of drug discovery and development for finding treatments for diseases with unmet medical needs).

11 *Id.*; *See* Michael B. Bracken, *Why Animal Studies are Often Poor Predictors of Human Reactions to Exposure*, 101 J. ROYAL SOC'Y MED. 120, 120-121 (2008) (explaining the long-recognized difficulties inherent in extrapolating drug data from animals).

12 FDA Modernization Act 2.0, Pub. L. No. 117-328, § 3209, 125 (2022).

13 FDA Modernization Act 2.0 § 3209.

14 Nierode, *supra* note 10, at 213–14.

15 *See generally* Lorna Ewart et al., *Performance Assessment and Economic Analysis of a Human Liver-Chip for Predictive Toxicology*, 2 COMM'N MED. 154, 154–55 (2022) (discussing how the human Liver-Chip can improve drug development).

Act 3.0 is needed because the current system does not do enough to disincentivize animal-based testing that is unnecessarily expensive, unjustifiably delays new drug development, and inadequately ensures safety for humans.

Part II of this Article discusses the history of animal testing in biomedical research. Part II, Section A introduces the first law regulating pre-market approval of new drugs—the 1938 Federal Food, Drug, and Cosmetics Act—which ushered in an era of mandatory animal testing. Part II, Section B then explores the impact that animal testing has on animals themselves. Part III, Section A analyzes the safety problems generated from testing drugs meant for humans on animals. Part III, Section B shows how the FDA Modernization Act 2.0 has changed drug testing processes for the better by eliminating the legal requirement for animal-based testing. Part III, Section C describes how drug testing protocols can be safer, cheaper, and quicker by ensuring that drug testing is human-centered and not animal-centered. Part III, Section D proposes an "FDA Modernization Act 3.0" to perfect the transition from animal-centered testing to human-centered testing. Finally, Part III, Section E addresses the opposition to ending animal testing by showing that reliance on it is largely based on entrenchment rather than necessity.

II. BACKGROUND

Animals have been used throughout the history of biomedical research. Starting as early as 384 BCE, Greek physician-scientists such as Aristotle and Erasistratus performed animal experiments.[16] However, back then, the use of animals had less to do with their presumption as a good test subject and more to do with cultural norms; dissecting human cadavers was taboo.[17]

By the twelfth century, animals were used to test surgical procedures before performing them on human patients.[18] But, it has been understood since early on that animals are not a sufficient substitute for humans. For example, Flemish physician and surgeon Vesalius realized that many anatomical structures present in animals that were assumed to exist in humans as well were not there.[19] In fact, because of this realization, Vesalius broke established civil and religious rules to illegally dissect human cadavers.[20]

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16 Rachel Hajar, *Animal Testing and Medicine*, 12(1) HEART VIEWS 42, 42 (Mar. 2011).

17 Nuno Henrique Franco, *Animal Experiments in Biomedical Research: A Historical Perspective*, 3 ANIMALS (BASEL) 238, 239 (Mar. 19, 2013).

18 Hajar, *supra* note 16, at 42.

19 Franco, *supra* note 17, at 240.

20 *Id.*

A. 1938 FEDERAL FOOD, DRUG, AND COSMETIC ACT

Despite the notable differences between humans and animals, animal testing has long been utilized in the United States for drug research.[21] For most of that history, researchers could perform animal and human experiments with relative freedom and few limitations.[22] Early United States law did not require that drugs be approved by any government entity for them to be sold to the public. [23] Drug disasters in the early United States abounded.[24] One such disaster involved the drug Elixir Sulfanilamide, which was marketed to pediatric patients in 1937.[25] A chemical analogue to antifreeze, it killed more than 100 people.[26]

In reaction, Congress enacted its first real drug testing law.[27] That law, the 1938 Federal Food, Drug, and Cosmetic Act, mandated that manufacturers demonstrate drug safety *before* drugs could be sold.[28] The result was a standard that new drugs undergo animal testing to prove their safety.[29]

B. THE IMPACT OF ANIMAL TESTING ON ANIMALS

A vital component of analyzing animal-based testing is its impact on the animals themselves. Although the focus of this Article is on the scientific complications with animal testing, it is impossible not to consider the individual suffering that animals are forced to endure in the process. Accordingly, to fully inform researchers, legislators, and potential consumers on the moral implications of animal testing, this Article looks to the full life cycle of animals used to test drugs.

i. Species Used in Research

Each year over one-hundred million animals are used in research experiments in the United States.[30] The true number is unknown, however, because laboratories are not legally required to disclose data about

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21 Hajar, *supra* note 16, at 42.

22 Jeri Sechzer, *Historical Issues Concerning Animal Experimentation in the United States*, 15 F Soc. Sci. Med., 13, 15–16 (1981).

23 *Part II: 1938, Food, Drug, Cosmetic Act*, U.S. Food & Drug Admin. (Nov. 27, 2018), https://www.fda.gov/about-fda/changes-science-law-and-regulatory-authorities/part-ii-1938-food-drug-cosmetic-act (accessed Jan. 16, 2024).

24 *Id.*

25 *Id.*

26 *Id.*

27 *Id.*; 21 U.S.C. § 301.

28 *Part II: 1938, Food, Drug, Cosmetic Act*, *supra* note 23.

29 Peter-James H. Zushin et al., *FDA Modernization Act 2.0: Transitioning Beyond Animal Models with Human Cells, Organoids, and AI/ML-Based Approaches*, 133(21) J. Clinical Investigation 1, 1 (2023).

30 Larry Carbone, *Estimating Mouse and Rat Use in American Laboratories by Extrapolation from Animal Welfare Act-Regulated Species*, 11, 16 Sci. Rep. (2021).

all animals used in experimentation.[31] Additionally, millions of genetically modified 'surplus' animals are produced—to ensure that short-notice demand is quickly met—that are not used in experiments.[32] When demand does not rise to require their use, surplus animals are killed.[33]

There are no federal drug testing laws in the United States that limit the species of animal that may be used.[34] The most commonly used species are mice, rats, fish, and birds.[35] Other common species include nonhuman primates, dogs, cats, pigs, guinea pigs, and rabbits.[36] Beagles are the most common dog breed utilized in laboratory research; they are favored because their temperament is so compliant.[37]

In a singular move in 2015, the National Institutes of Health voluntarily ended testing on chimpanzees in their research due to morality concerns with experimenting on our closest relatives.[38] The agency promised to send the last of its research chimpanzees to sanctuaries.[39] However, various species of other nonhuman primates are currently used in federal drug research.[40] And, all nonhuman primates are still legally permitted to be tested on at private facilities.[41] A 2017 Fish and Wildlife Service rule makes it more difficult for private labs to test specifically on chimpanzees—but without laws in place to cement that decision, it is possible for chimpanzee testing to restart.[42]

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[31] *Id.* at 11.

[32] Hartmut Wewetzer et al., *The Fate of Surplus Laboratory Animals*, 24(3) EMBO REP. 1, 1 (2023) https://www.embopress.org/doi/full/10.15252/embr.202256551 (accessed Feb. 8, 2024).

[33] *Id.*

[34] *See Animals in Science*, AM. ANTI-VIVISECTION SOC'Y, https://aavs.org/animals-science/animals-used/ (accessed Jan. 28, 2024) (the use of *species* protected under the Endangered Species Act may be restricted).

[35] *See generally* Adriana Dominguez-Oliva et al., *The Importance of Animal Models in Biomedical Research: Current Insights and Applications*, 13 ANIMALS (BASEL) 1223 (Mar. 31, 2023).

[36] *Id.*

[37] *Animals in Laboratories*, NAT'L HUMANE EDUC. SOC'Y, https://www.nhes.org/animals-in-laboratories/ (accessed Jan. 21, 2024).

[38] Francis S. Collins, *NIH Will No Longer Support Biomedical Research on Chimpanzees*, NAT'L INSTS. HEALTH (Nov. 17, 2015), https://www.nih.gov/about-nih/who-we-are/nih-director/statements/nih-will-no-longer-support-biomedical-research-chimpanzees (accessed Jan. 21, 2024).

[39] *Id.*; However, the agency did not immediately (or even delayed) release chimpanzees to sanctuary. See *Humane Soc'y of the United States v. Nat'l Institutes of Health*, No. 21-CV-00121-LKG, 2022 WL 17619232, *1–2 (D. Md. Dec. 13, 2022) (in fact, animal protection organizations sued the agency to seek the freedom of languishing, and non-utilized, chimpanzees).

[40] *Nonhuman Primate Models in Biomedical Research*, NAT'L ACADS. SCIS., ENG'G, & MED (May 4, 2023), https://www.ncbi.nlm.nih.gov/books/NBK591440/.

[41] *Supra* note 34.

[42] *Animal Testing: Models for Improvement*, ANIMAL LEGAL DEF. FUND, https://aldf.org/article/animal-testing-models-for-improvement/ (accessed Mar. 5, 2024).

ii. Legal Coverage

The Animal Welfare Act regulates the treatment of animals by dealers and in privately and publicly funded research and testing facilities.[43] Both the Animal Welfare Act and the Health Research Extension Act, codified in the Public Health Services Act, regulate the use of animals for publicly funded research projects.[44] The Animal Welfare Act is enforced by the Animal and Plant Health Inspection Service, which is a part of the United States Department of Agriculture.[45] The Health Research and Extension Act is enforced by the Office of Laboratory Animal Welfare, under the National Institutes of Health, within the Department of Health and Human Services.[46]

The Animal Welfare Act contains a convoluted definition of the word "animal," in that it is not synonymous with the standard use of the word. In the Act, "animal" is defined as "any live or dead dog, cat, monkey (nonhuman primate mammal), guinea pig, hamster, rabbit, or such other warm-blooded animal, as the Secretary [of Agriculture] may determine is being used, or is intended for use, for research, testing, experimentation, or exhibition purposes, or as a pet."[47] The definition specifically excludes certain animals bred for research purposes from the definition of "animal," including: rats of the genus *Rattus*, mice of the genus *Mus*, birds, fish, reptiles, and farmed animals.[48] The Public Health Service Policy defines "animal" as "[a]ny live, vertebrate animal used or intended for use in research, research training, experimentation, or biological testing or for related purposes."[49] Taken together, these definitions mean that about 95% of the animals used in research do not qualify as an animal and accordingly do not receive legal protections.[50]

iii. Acquisition and End of Life

Laboratories must obtain animals from licensed dealers, which are classified under the Animal Welfare Act as either Class A or Class B

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43 Animal Welfare Act, 7 U.S.C. § 2131 (2015).

44 Health Research Extension Act of 1985, 42 U.S.C. § 201.

45 *Animal Welfare Act*, Nat'l Agric. Libr., https://www.nal.usda.gov/animal-health-and-welfare/animal-welfare-act (accessed Jan. 14, 2024).

46 *About Us*, Nat'l Insts. Health, https://olaw.nih.gov/about-us.htm (accessed Jan. 21, 2024).

47 7 U.S.C. § 2132(g).

48 *Federal Laws and Agencies Involved With Animal Testing*, Animal Legal Def. Fund, https://aldf.org/article/federal-laws-and-agencies-involved-with-animal-testing/ (accessed Jan. 22, 2024).

49 U.S. Dep't Health & Hum. Services & Nat'l Insts. Health, No. 15-8013, Public Health Service Policy on Humane Care and Use of Laboratory Animals 8 (2015) [hereinafter PHS Policy].

50 *Federal Laws and Agencies Involved With Animal Testing*, Animal Legal Def. Fund, https://aldf.org/article/federal-laws-and-agencies-involved-with-animal-testing/ (accessed Jan. 14, 2024).

licensees.[51] Class A licensees maintain their own breeding colonies.[52] Class B licensees obtain *random source* animals, then resell them.[53] In states that allow pound seizure, Class B licensees can obtain animals, including cats and dogs, from animal shelters.[54] According to a government report, in a one-year period 20.4% of dogs and 60.9% of cats acquired by Class B licensees came from animal shelters.[55] 30.8% and 21.4%, respectively, were acquired from other licensees and registrants (*i.e.* other Class B licensees).[56] And, 48.8% and 17.7%, respectively, were acquired from individuals (*i.e.* hobby breeders).[57]

At the end of their use, animals are usually killed.[58] Options allowing release are extremely limited; many animals are genetically modified, and that, combined with their sheer number, makes release unlikely.[59] For the miniscule number of domestic animals that survive relatively unscathed, adoption is possible.[60]

iv. Caging

Applicable laws set minimum requirements for the enclosures that animals subject to testing live in. Specifics vary by species, but generally, primary enclosures must: be structurally sound to protect the animal from injury, provide convenient access to food and water, be clean and free of feces, and be an appropriate temperature.[61] The space afforded to each animal is minimal. For example, rabbits weighing more than 11.9 pounds are only required to have five square feet of space to live their entire life in.[62] Enrichment—the provision of objects, foods, or interactions for an animal to express their natural activities—is only required for nonhuman primates.[63] Exercise is only required for dogs.[64]

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51 9 C.F.R. § 1.1 (2024); 9 CFR § 2.1(a)(1).

52 9 C.F.R. § 1.1.

53 *See* 9 C.F.R. § 1.1; 9 C.F.R. § 2.133 ("Random source means dogs and cats obtained from animal pounds or shelters, auction sales, or from any person who did not breed and raise them on his or her premises.").

54 9 C.F.R. § 2.132.

55 Comm. on Sci. & Humane Issues in the Use of Random Source Dogs & Cats in Rsch., Nat'l Rsch. Council of the Nat'l Acads., Scientific and Humane Issues in the use of Random Source Dogs and Cats in Research 74–75 (The Nat'l Academies Press ed., 2009) [hereinafter Comm. on the Use of Random Source].

56 *Id.*

57 *Id.*

58 Hemi Kim, *What Happens to Lab Rats After Testing?*, Sentient Media (Dec. 10, 2021), https://sentientmedia.org/what-happens-to-lab-rats-after-testing/ (accessed Jan. 14, 2024).

59 *Id.*

60 *Id.*

61 Animal & Plant Health Inspection Serv., Animal Welfare Act and Animal Welfare Regulations (Blue Book) 140 (July 2023).

62 *Id.* at 187.

63 *Id.* at 212.

64 *Id.* at 145.

The consequence of such narrowly targeted laws is that animals' cages bear little to no resemblance to their natural habitat. The cages do not let the animals act out their natural behaviors and accordingly are scientifically inappropriate. These poor environmental conditions can also impact the efficacy of tests conducted upon them.[65] Biologists have learned that cage amendments can lead to vast changes in the neurobiology, behavior, immune responses, disease resistance, and cancer remission of captive mice and rats.[66] Because environmental effects may impose such huge impacts on biomedical research, at least one scholar has called for research animals to live in the wild or roam free in captive environments.[67]

v. Experiments

Regarding testing methods, there are no federal laws limiting the types of experiments that can be conducted upon animals used in research. No matter how painful, or how long an experiment causes an animal to suffer until a result may be observed, laboratory research can proceed. In other words—and as the Animal Welfare Act provides—pain relief should be provided but can be withheld when scientifically necessary.[68] Again, these minimal protective regulations only apply to animals that fit within the legal definition of "animal," which excludes the vast majority of them.

Despite that, industry participants tout use of the *3Rs Principle*.[69] The 3Rs Principle promotes reduction, refinement, and replacement of animal-based research whenever researchers find it scientifically appropriate.[70] Although in theory this promotes a sound ideal, the 3Rs Principle is not federally required.[71] Publicly-funded facilities must utilize the Guide for the Care and Use of Laboratory Animals (the Guide) as a basis for developing and implementing their activities involving animals.[72] The Guide includes the 3Rs, but all of its guidance boils

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65 Garet Lahvis, *Unbridle Biomedical Research from the Laboratory Cage*, ELIFE SCI. 1, 1, 6 (2017).

66 *Id.* at 1.

67 *Id.* at 4.

68 7 U.S.C. § 2143(a)(3)(C)(v) (the phrase "scientifically necessary" is not defined in the Animal Welfare Act).

69 Comm. on the Use of Random Source, *supra* note 55, at 47; *see also Animals Used in Research*, PFIZER, https://www.pfizer.com/science/clinical-trials/integrity-and-transparency/animals-used-in-research (describing that their animal testing policy is based on the 3Rs Principle) (accessed Jan. 15, 2024).

70 Comm. on the Use of Random Source, *supra* note 55, at 47.

71 PHS POLICY, *supra* note 49 at 9; *see generally* COMM. FOR THE UPDATE OF THE GUIDE FOR THE CARE AND USE OF LAB'Y ANIMALS & INST. FOR LAB'Y ANIMAL RSCH., GUIDE FOR THE CARE AND USE OF LABORATORY ANIMALS (8th ed. 2011) (referencing the 3Rs throughout, but utilizing discretionary language like *shall be considered* and *should)*.

72 PHS POLICY, *supra* note 49, at 9.

down to recommendations.[73] Privately-funded facilities have no obligation to follow the 3Rs.[74]

Two more important caveats remain. First, publicly-funded research facilities must submit *written assurance* that they utilized the Guide.[75] No government official may dictate researchers' testing plans.[76] Accordingly, if researchers prefer to utilize animal testing (even if better alternatives exist), neither reduction, refinement, nor replacement is required.

Second, at both privately-funded and publicly-funded facilities, no legal requirement prohibits research methods that are tantamount to torture, so long as researchers consider any information gained from the research to be scientifically relevant.[77] This is particularly true if the researchers are studying pain, chronic issues, and long-term impacts.[78]

III. ANALYSIS

Signed into law on December 29, 2022, the FDA Modernization Act 2.0[79] represents a landmark change in drug testing protocols and animal testing practices.[80] For the first time since 1938, animal testing is no longer mandatory for drug development.[81] While scientific developments are largely responsible for this change in policy,[82] it is also a recognition of the moral issues with animal experimentation.

The FDA Modernization Act 2.0 was introduced by Senators Rand Paul (R-KY) and Cory Booker (D-NJ)—along with ten co-sponsors—as Senate Bill 5002.[83] It passed the Senate unanimously and without amendment.[84] In reference to the Bill, Senator Paul, a medical doctor in his own right, said:

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73 *Supra* note 71.

74 PHS POLICY, *supra* note 49, at 9 (the only covered activities are those conducted or supported by the Public Health Service).

75 PHS POLICY, *supra* note 49, at 9.

76 Paul Locke, *Laboratory Animal Law in the United States: Past, Present and Future*, THE BROOKS INST., at 32:56, https://thebrooksinstitute.org/resources/videos/animal-law-fundamentals/laboratory-animal-law-united-states-past-present-and (accessed Jan. 17, 2024).

77 *See* 7 U.S.C. § 2143(a)(3) (1970) (permitting, for example, "the withholding of tranquilizers, anesthesia, analgesia, or euthanasia when scientifically necessary"); PHS POLICY, *supra* note 49, at 13–14.

78 *Id.*

79 Jason J. Han, *FDA Modernization Act 2.0 Allows for Alternatives to Animal Testing*, 47 ARTIFICIAL ORGANS 449, 449 (2023).

80 *Congress Approves Landmark Measure to Reduce Animal Testing*, GLOBENEWSWIRE (Dec. 23, 2022), https://www.globenewswire.com/news-release/2022/12/23/2579295/0/en/Congress-Approves-Landmark-Measure-to-Reduce-Animal-Testing.html (accessed Jan. 5, 2024).

81 Han, *supra* note 79, at 449.

82 *Id.*

83 S. 5002, 117th Cong. (2022) (enacted).

84 168 CONG. REC. S5514 (daily ed. Sept. 29, 2022).

> The FDA Modernization Act 2.0 will accelerate innovation and get safer, more effective drugs to market more quickly by cutting red tape that is not supported by current science, and I'm proud to have led the charge. The passage of this bipartisan bill is a step toward ending the needless suffering and death of animal test subjects. . .[85]

Senator Booker provided: "[t]he passage of my bill will avoid the needless suffering of countless animals, now that experimental drug testing can be done with modern non-animal alternatives that are more scientifically relevant."[86] His press release on the issues noted that "science and data has shown that in some products, animal testing is a highly inconsistent predictor of toxic responses in humans. . ."[87] Further, he recognized that in recent years, non-animal tests have been developed that are more predictive of human drug responses.[88]

A. THE EFFICACY OF TESTING DRUGS ON ANIMALS

It is widely accepted that drug testing methods should be evidence based. At the onset of drug trials, experimenters believed a drug's impact on animals could accurately predict the drug's impact on humans.[89] However, drugs successfully tested on animals have approximately a 90% failure rate in humans.[90] Notably, the failure rate for drugs that are meant to target major neurodegenerative disorders approaches 100%.[91] Studies show that adverse drug reactions may be responsible for the deaths of more than 100,000 people in the United States each year.[92] That would make adverse drug reactions the fourth leading cause of death for Americans, which is more than deaths caused by pulmonary disease, diabetes, pneumonia, accidents, and car accidents.[93] In fact, a recent analysis found that, out of ninety-three adverse drug reactions,

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85 Press Release, Rand Paul, Senate Passes Paul, Booker Bipartisan FDA Modernization Act 2.0 to End Animal Testing Mandates (Sept. 29, 2022), https://www.paul.senate.gov/news-senate-passes-paul-booker-bipartisan-fda-modernization-act-20-end-animal-testing-mandates/ (accessed Jan. 5, 2024).

86 Press Release, Cory Booker, United States Senator, Booker Celebrates Passage of FDA Modernization Act to Ban Animal Testing Mandates (Sept. 22, 2022), https://www.booker.senate.gov/news/press/booker-celebrates-passage-of-fda-modernization-act-to-ban-animal-testing-mandates (accessed Jan. 5, 2024).

87 *Id.*

88 *Id.*

89 Franco, *supra* note 17, at 246.

90 *A New Path to New Drugs: Finding Alternatives to Animal Testing*, SCIENCE (Sept. 1, 2023), https://www.science. org/content/resource/new-path-new-drugs-finding-alternatives-to-animal-testing#:~:text=Organ-on-a-chip&text=By%20stringing%20organ-on-a,without%20preclinical%20animal%20efficacy%20data (accessed Jan. 5, 2024).

91 *Id.*

92 *Preventable Adverse Drug Reactions: A Focus on Drug Interactions*, U.S. FOOD & DRUG ADMIN. (Mar. 6, 2018), https://www.fda.gov/drugs/drug-interactions-labeling/preventable-adverse-Drug-reactions-focus-drug-interactions#ADRs:%20Prevalence%20and%20Incidence (accessed Jan. 5, 2024).

93 *Id.*

only 19% could have been predicted by animal testing.[94] To fully inform the proper place of animal testing in new drug development, this Section will analyze three topics: (1) when drugs that *are* safe for animals *are not* safe for humans; (2) when drugs that *are not* safe for animals *are* safe for humans; and (3) when animal testing unnecessarily and harmfully slows down drug approval. Together, these examples show that preclinical animal testing has dangerous consequences for human consumers.

i. When Drugs That Are Safe for Animals Are Not Safe for Humans

A shockingly high percent of all drugs shown to be safe in animal tests fail in human trials as ineffective or dangerous.[95] To exemplify the dangerous conclusions that 'successful' animal trials can lead to, the following is a non-exhaustive list of negative health impacts on humans that occurred *after* the drug passed animal tests:

a. Isuprel, a treatment for asthma, caused over 3,500 human deaths.[96] It was tested on rats, guinea pigs, dogs, and monkeys—all of which had received doses far exceeding those administered in humans.[97]
b. TGN1412, a treatment for autoimmune disease, was given—at 1/500th the dose found safe in animal testing—to six human volunteers.[98] Within minutes, all the volunteers were critically ill, and afterward, all were left with long-term complications.[99]
c. BIA-102474-101, a treatment for a range of disorders from anxiety to Parkinson's, was given—at 1/500th dose found safe in dogs—to human volunteers.[100] It caused all of them to experience deep brain hemorrhage and necrosis.[101] One volunteer died.[102]
d. Fialuridine, a treatment for hepatitis B, caused the deaths of five volunteers during clinical trials.[103] Two other volunteers only survived after receiving liver transplants.[104] It had previously been tested on mice, rats, dogs, monkeys, and woodchucks in doses that were hundreds of times higher than the doses given to humans.[105]

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94 Peter van Meer et al., *The Ability of Animal Studies to Detect Serious Post Marketing Adverse Events is Limited*, 64 REGUL. TOXICOLOGY & PHARMACOLOGY 345, 348 (Dec. 2012).

95 *A New Path to New Drugs: Finding Alternatives to Animal Testing*, *supra* note 90.

96 Van Norman, *supra* note 6, at 846.

97 *Id.*

98 *Id.* at 847.

99 *Id.*

100 *Id.*

101 *Id.*

102 *Id.*

103 Dan Xu et al., *Fialuridine Induces Acute Liver Failure in Chimeric TK-NOG Mice: A Model for Detecting Hepatic Drug Toxicity Prior to Human Testing*, 11 PLOS MED. 1, 2 (Apr. 15, 2014).

104 *Id.*

105 *Id.*

ii. When Drugs That Are Not Safe for Animals Are Safe for Humans

On the opposite side of the spectrum, when animal tests falsely identify a safe drug as toxic to humans, the likely outcome is abandonment of further development.[106] Many potentially beneficial drugs have undoubtedly failed animal testing and therefore never reached patients that needed help.[107] Because a drug that shows any toxicity when it is tested on animals is unlikely to ever make it to the stage of human testing, the true scale of this drawback cannot be fully known.[108] Thankfully, some drugs—that certainly would have failed clinical animal testing—were developed prior to the requirements, allowing them to help humans.[109] Some examples include: (1) penicillin, which is fatal to guinea pigs; (2) Aspirin, which is toxic to rats and rhesus monkeys; and (3) acetaminophen (also known as paracetamol, and brand name Tylenol) which is toxic to dogs and cats.[110]

iii. When Animal Testing Unnecessarily and Harmfully Slows Down Drug Approval

Sometimes, animal testing requirements unnecessarily delay development of beneficial drugs. HIV/AIDS vaccine research represents one of these most notable failures.[111] That vaccine research dedicated decades to testing on a swath of animal species, including chimpanzees.[112] Despite animal tests yielding about 90 promising vaccines, they all failed in humans.[113] Of note, one of the vaccines failed to neutralize HIV grown and tested in cell culture, but because it protected chimpanzees from HIV infection, researchers took two late-phase clinical trials.[114] And again, once tested in humans, that vaccine failed.[115]

The National Institutes of Health's 2016–2020 Strategic Plan explains that "[p]etri dish and animal models often fail to provide good ways to mimic disease or predict how drugs will work in humans, resulting in much wasted time and money while patients wait for therapies."[116] Together, these examples show that animal testing can be a time-consuming, expensive, and unnecessary tangent.

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106 Van Norman, *supra* note 6, at 847.

107 *Id.*

108 *Id.*

109 *Id.*

110 *Id.*

111 Aysha Akhtar, *The Flaws and Human Harms of Animal Experimentation*, 24 CAMBRIDGE Q. HEALTHCARE ETHICS 407, 412 (Oct. 2015).

112 *Id.*

113 *Id.*

114 *Id.*

115 *Id.*

116 NAT'L INSTS. HEALTH, NIH-WIDE STRATEGIC PLAN: FISCAL YEARS 2016-2020 38 (2015).

B. DRUG TESTING UNDER THE FDA MODERNIZATION ACT 2.0

Although the 1938 Federal Food, Drug, and Cosmetic Act has been substantially amended since its enactment, it still retains its basic structure.[117] Today, it remains the preeminent federal law regulating prescription and non-prescription drugs.[118] The 1938 version of the Act did not explicitly require animal testing.[119] It did, however, mandate that drugs be shown to be safe before their commercial sale.[120] Additionally, it required that new drug applications be filed with the Food and Drug Administration (the Administration), which would analyze drug applications' data and make a determination on its safety.[121] As part of its drug safety review, the Administration could request animal studies.[122] Still, it was not until 1961 that the Administration exercised its authority to regulate clinical trials.[123]

In 1962, animal testing requirements were written into the Federal Food, Drug, and Cosmetic Act.[124] After that, the Administration felt more confident regulating such trials.[125] Then, "new regulations prohibited testing a drug in humans until preclinical studies could predict that the drug could be given safely to people."[126] The Administration required sponsors "to submit 'reports of pre-clinical tests (including tests on animals) of such drug adequate to justify proposed clinical testing.'"[127] As such, the state of administrative requirements was tantamount to a statutory mandate for animal testing.

The Food and Drug Administration application process for new prescription drugs follows five steps.[128] First is the discovery and

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117 CONG. RSCH. SERV., R43609, ENFORCEMENT OF THE FOOD, DRUG, AND COSMETIC ACT: SELECT LEGAL ISSUES 3 (updated Feb. 9, 2018).

118 *Id.*

119 *See* Federal Food, Drug, and Cosmetic Act, Pub. L. No. 75-717, § 505, 52 Stat. 1040, 1052 (1938) (codified as amended at 21 U.S.C § 301) (outlining testing requirements for new drugs). Some scholars assert that the 1938 Federal Food, Drug and Cosmetic Act mandated animal testing. *See, e.g.,* Doortje Swaters et al., *A History of Regulatory Animal Testing: What Can We Learn?*, 50 ALTERNATIVES TO LAB'Y ANIMALS 324, at 324 (Sept. 2022) ("The Act made it a requirement that safety and efficacy data, including data from animal tests, be provided to the FDA . . ."). However, review of the 1938 Federal Food, Drug & Cosmetics Act does not reveal any such mandate. The word "animal" does not appear in the relevant section of the 1938 Act (nor does any synonym).

120 Federal Food, Drug, and Cosmetic Act § 505; Suzanne White Junod, *FDA and Clinical Drug Trials: A Short History*, U.S. FOOD & DRUG ADMIN., https://samizdathealth.org/wp-content/uploads/2020/12/FDA-and-RCTs.pdf (accessed Jan. 20, 2024).

121 Federal Food, Drug, and Cosmetic Act § 505; Junod, *supra* note 120.

122 Junod, *supra* note 120.

123 *Id.*

124 Drug Amendments of 1962, Pub. L. No. 87–781, §§ 505, 507, 76 Stat. 780, at 783, 787 (1962).

125 Junod, *supra* note 120.

126 *Id.*

127 27 Fed. Reg. 7990; *see also* Junod, *supra* note 120.

128 *The Drug Development Process*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/patients/learn-about-drug-and-device-approvals/drug-development-process (accessed

development step.[129] At this stage, researchers have thousands of drug compounds to test which may become candidates for further development.[130] After this, only a small amount of compounds will look promising enough to warrant further study.[131] Those promising compounds undergo further experimentation to gather information regarding: "how the compound is absorbed, distributed, metabolized, and excreted; its potential benefits and mechanisms of action; the best dosage; the best way to give the drug (such as by mouth or injection); side effects or adverse events []; how it affects different groups of people (such as by gender, race, or ethnicity); how it interacts with other drugs and treatments; and its effectiveness as compared with similar drugs."[132]

The second step is preclinical research.[133] This step occurs before selected drugs are tested on humans, allowing researchers to determine dosing and potential for serious harm—also called toxicity.[134] After reviewing preclinical testing results, including animal tests, researchers determine whether drugs should enter the next stage and be tested on humans.[135] In preclinical studies, the Food and Drug Administration requires researchers use the Good Laboratory Practices (The Practices).[136] The Practices are meant to ensure the integrity and reliability of laboratory studies,[137] by setting guidelines for organization, personnel, facilities, equipment, conduct, and documentation.[138]

The Practices set no welfare standards geared toward the comfort or enrichment of animals. Instead, animal controls are designed to ensure studies are not contaminated or skewed by basic animal needs.[139] For example, the Practices provide that animals used in different studies should not be housed together in order to avoid inadvertent drug

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Jan. 18, 2024). Note that over-the-counter drugs that meet a monograph (certain preestablished conditions such as active ingredients, uses, doses, routes of administration, and labeling) do not require preapproval to be sold. Over-the-counter drugs that do not fit a monograph follow the same process as new prescription drugs. *See OTC Drug Review Process | OTC Drug Monographs*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/otc-drug-review-process-otc-drug-monographs (accessed Jan. 18, 2024) (describing the regulatory pathways for over-the-counter drugs, with an emphasis on over-the-counter drug monographs).

129 *The Drug Development Process*, *supra* note 128.

130 *Step 1: Discovery and Development*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/patients/drug-development-process/step-1-discovery-and-development (accessed Jan. 18, 2024).

131 *Id.*

132 *Id.*

133 *The Drug Development Process*, *supra* note 128.

134 *Step 2: Preclinical Research*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/patients/drug-development-process/step-2-preclinical-research (accessed Jan. 18, 2024).

135 *Id.*

136 *Id.*; 21 C.F.R. §§ 58.1–58.219.

137 21 C.F.R. §§ 58.1(a), 58.81(a).

138 *See* 21 C.F.R. §§ 58.29–58.190.

139 21 C.F.R. § 58.43(a).

exposure that could impact the result of the studies.[140] The Practices further require standard operating procedures for the housing, feeding, handling, and care of animals, but allow researchers to set those standards.[141] The Practices also allow animals to be treated for disease, but only if such treatment "does not interfere with the study."[142]

The third step is clinical research. Clinical research refers to studies or trials that are done in humans.[143] In this step, developers design a clinical study around the selected drug in order to answer specific questions that they have.[144] They also begin the Investigational New Drug Process, where developers provide the Food and Drug Administration with the following: animal study data and toxicity; manufacturing information; clinical protocols (study plans); data from any prior human research; and information about the investigator.[145] The Administration offers technical assistance, but developers are not required to take suggestions.[146]

The fourth step is Food and Drug Administration review. After all the previous steps, if a drug developer finds a drug that it proposes is safe and effective for its intended use, then the company files an application with the Administration for permission to market that drug.[147] The Administration's review team examines all submitted data on the drug and decides whether to approve it.[148]

Drugs that enter the market are continually subject to the fifth step: Food and Drug Administration post-market safety monitoring.[149] Here, the Administration reviews reports of problems with drugs.[150] Ultimately, the Administration can add cautions to the dosage type and amount, to the usage information, or—for more serious issues that it finds—it can also add other measures.[151]

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140 21 C.F.R. § 58.90(e).

141 21 C.F.R. § 58.90(a).

142 21 C.F.R. § 58.90(c).

143 *Step 3: Clinical Research*, U.S. Food & Drug Admin., https://www.fda.gov/patients/drug-development-process/step-3-clinical-research (accessed Jan. 20, 2024).

144 *Id.*

145 *Id.*

146 *Id.*

147 *Step 4: FDA Drug Review*, U.S. Food & Drug Admin., https://www.fda.gov/patients/drug-development-process/step-4-fda-drug-review (accessed Jan. 20, 2024).

148 *Id.*

149 *Step 5: FDA Post-Market Drug Safety Monitoring*, U.S. Food & Drug Admin., https://www.fda.gov/patients/drug-development-process/step-5-fda-post-market-drug-safety-monitoring (accessed Jan. 20, 2024).

150 *Id.*

151 *Id.*

i. How the FDA Modernization Act 2.0 Changes Things

In a landmark change, the FDA Modernization Act 2.0 removes the statutory requirement that new drugs undergo animal testing. Legally, the FDA Modernization Act 2.0 accomplishes this by removing the requirement for "the submission . . . of preclinical tests (including tests on animals) . . . to justify the proposed clinical testing."[152] It replaces "preclinical tests" with "nonclinical tests."[153] It defines nonclinical tests to mean:

> . . . a test conducted in vitro, in silico, or in chemico, or a non-human in vivo test that occurs before or during the clinical trial phase of the investigation of the safety and effectiveness of a drug, and may include animal tests, or non-animal or human biology-based test methods, such as cell-based assays, microphysiological systems, or bioprinted or computer models.[154]

There are two notable aspects of this definition. First, animal testing remains an option. Still, the availability of nonclinical testing options that do not include animals represents a sea change in drug testing. Second, the language "and may include . . . non-animal or human biology-based test methods, such as" makes the list non-exhaustive. This allows researchers to determine what testing method best fits their needs. It will also allow alternative drug testing methods to continue progressing in time with advancing scientific discoveries.

ii. Nonclinical Testing Methods, Aside from Animal Testing

From a practical perspective, the FDA Modernization Act 2.0 impacts the two steps before the clinical trial phase—the discovery and development phase and the preclinical research phase—of the Food and Drug Administration new drug approval process.[155]

Utilizing human-centered alternatives in these steps in lieu of animal testing can lead to staggeringly improved results. For example, carcinogenicity tests on animals have an estimated prediction of human cancers of only 42%.[156] But, a combination of human cell-based tests increases detection rates to 90–95%.[157]

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[152] S. 5002, 117th Cong. § 2 (2022) (enacted); 21 U.S.C. § 355 (2011), *amended by* 21 U.S.C. § 355(i)(a) (2023).

[153] S. 5002, 117th Cong. § 2.

[154] *Id.*

[155] *Id.*

[156] *Cosmetics*, Cruelty Free Int'l, https://crueltyfreeinternational.org/make-change/cosmetics (accessed Jan. 21, 2024).

[157] Romualdo Benigni et al., *In Vitro Cell Transformation Assays for an Integrated, Alternative Assessment of Carcinogenicity: A Data-Based Analysis*, 21 Mutagenesis 107, 107 (Jan. 2013).

Human-centered alternatives to animal testing include:

a. **Cell-based assays**: Cell-based assays, or cell-based test systems, have been widely used in drug discovery research for decades.[158] They are two-dimensional tissues that utilize *in vitro* living humans cells to identify compounds that have a desired activity at the drug target.[159] They are also used to examine a drug's toxicity, safety profile, and efficacy.[160] Utilization of cell-based assays is effective because they are specifically designed for the drug compound being tested.[161] Typically, they are used at the very beginning stages of drug discovery.[162] Compared to animal testing, cell-based assays are beneficial because they can quickly and simultaneously test hundreds of thousands of promising lead compounds.[163]

b. **Organ chips**: Also called organs-on-a-chip, organ chips are transparent instruments that are roughly the size of AA batteries.[164] Within them are small channels that are lined with human cells.[165] Researchers utilize them by pumping drugs through the channels to simulate how the drug would interact in particular parts of the human body.[166]

Recently, organ chips have moved from single organ-level to organism-level functions.[167] By coupling two or more organ chips, human "body-on-chips" systems are made, which have the benefit of mimicking the entire body's physiology.[168] More impressively, body-on-chips

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158 Arun Kumar, *How Are Cell-Based Assays Useful in Drug Discovery Research?*, ENZO (Mar. 2021), https://www.enzolifesciences.com/science-center/technotes/2021/march/how-are-cell-based-assays-useful-in-drug-discovery-research?/ (accessed Jan. 21, 2024).

159 Nicole Gleichmann, *Assay Development: An Overview*, TECH. NETWORKS (updated Dec. 18, 2023), https://www.technologynetworks.com/drug-discovery/articles/assay-development-329953 (accessed Jan. 21, 2024); Fen Wei, Sicen Wang, and Xilan Gou, *A Review for Cell-Based Screening Methods in Drug Discovery*, 7 BIOPHYSICS REPORTS 504, 505 (Dec. 31, 2021), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10210057/ (accessed Feb. 11, 2024).

160 *Id.*

161 *Id.*

162 *Id.*

163 Kumar, *supra* note 158.

164 Alivia Kaylor, *Alternatives to Animal Testing Models in Clinical and Biomedical Research*, PHARMA NEWS INTEL. (Feb. 1, 2023), https://pharmanewsintel.com/features/alternatives-to-animal-testing-models-in-clinical-and-biomedical-research (accessed Jan. 19, 2024).

165 Emily Anthes, *Could the Next Blockbuster Drug Be Lab-Rat Free?*, N.Y. TIMES (Mar. 7, 2023), https://www.nytimes.com/2023/03/07/health/drug-animals-testing.html (accessed Jan. 19, 2024).

166 *Id.*

167 Donald E. Ingber, *Human Organs-on-Chips for Disease Modelling, Drug Development and Personalized Medicine*, 23 NATURE REV. GENETICS 467, 467 (Aug. 2022).

168 *Id.*

can be personalized for distinct genetic subpopulations, subgroups with particular disease comorbidities, and even individual patients.[169]

Unlike animal testing, organ chips have the advantage of mimicking the *human* body. For example, in a recent study, the biotech company Emulate re-screened twenty-seven well-studied drugs.[170] They did so because even though those drugs had passed animal testing, some turned out to cause liver toxicity in humans.[171] When Emulate utilized liver-on-a-chips to rescreen those drug, the chips successfully flagged 87% percent of the toxic compounds.[172] In a statement about organ-on-a-chip technologies, Dr. Francis Collins, former Director of the National Institutes of Health, postulated that organ chip technologies would soon "mostly replace animal testing for drug toxicity . . . giving results that are more accurate, at lower cost and with higher throughput."[173]

c. **Organoids**: Organoids are three-dimensional tissues that mimic an organ's important functional, structural, and biological complexities.[174] They typically come from stem cells and can organize themselves into structures that resemble miniature organs.[175] Compared to animal models, organoids enable patient specificity and are more accessible for in-depth biological studies.[176] Disease-specific organoids provide the exclusive opportunity to mimic human diseases.[177]

The benefits of utilizing organoids became apparent during the COVID pandemic, when organoids showed their use for faster drug development.[178] One study on this topic revealed that organoids are "rapid-to-set-up, robust in scaling up, and ideal for genetic manipulation and personalization."[179] It also found that organoids are an attractive strategy for clinical applications as well as acting as a bridge between basic research and clinical practice.[180]

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169 *Id.*

170 Ewart et al., *supra* note 15, at 2.

171 *Id.* at 11.

172 *Id.* at 13.

173 *Hearing on FY2017 National Institutes of Health Budget Request Before the S. Comm. on Appropriations,* 114th Cong. at 34:14 (2016) (statement of Dr. Francis Collins).

174 Zixuan Zhao et al., *Organoids*, Nat. Revs. Methods Primers, Dec. 1, 2022, at 2, https://www.nature.com/articles/s43586-022-00174-y (accessed Feb. 3, 2024).

175 Javier Barbuzano, *Organoids: A New Window into Disease, Development, and Discovery,* Harvard Stem Cell Inst. (Nov. 7, 2017), https://hsci.harvard.edu/organoids (accessed Jan. 25, 2024).

176 Zhao, *supra* note 174, at 2.

177 Chrianjay Mukhopadhyay & Manash K. Paul, *Organoid-Based 3D in Vitro Microphysiological Systems as Alternatives to Animal Experimentation for Preclinical and Clinical Research*, 97 Archives of Toxicology 1429, 1429–30 (Mar. 14, 2023).

178 *Id.* at 1430.

179 Ria Sanyal & Manash K. Paul, *Organoid Technology and the COVID Pandemic*, *in* SARS-COV-2 Origin and COVID-19 Pandemic Across the Globe, 75, 76 (Vijay Kumar ed., Intechopen Limited, 2021).

180 *Id.*

d. **Computer models**: Computer modeling has been utilized in drug research for years.[181] Advances in computing technology and artificial intelligence make the technology increasingly powerful and sophisticated.[182] Computer models can predict whether a compound with certain chemical characteristics is likely to be toxic, how quickly compounds will be metabolized, and how a compound will be distributed in the body.[183] Similar to organ chips, and differing from animal testing, computer models can be adjusted to represent individual patients and different subgroups of patients.[184] For example, a computer model can test whether a medication that works in young adults would be safe and effective in older adults, who often have reduced kidney function.[185]

The increased utility of computer models is becoming more apparent as the technology progresses. Computer models of human heart cells show distinct promise.[186] In fact, one study out of the University of Oxford concluded that computer model heart cells were better than animal models at predicting whether dozens of known drugs would cause heart problems in humans.[187]

iii. Animal Welfare Reporting Requirements

This Article, infra, proposes adding new reporting requirements for drug development that utilizes animal testing. Because of that, background on the current reporting requirements is helpful. Under

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181 Richard Van Noorden, *Software Improves Toxicity Tests,* 559 NATURE 163, 163 (July 12, 2018), https://media.nature.com/original/magazine-assets/d41586-018-05664-2/d41586-018-05664-2.pdf (accessed Jan. 19, 2024).

182 Thomas Hartung, *Predicting Toxicity of Chemicals: Software Beats Animal testing*, EUROPEAN FOOD SAFETY AUTH. J at 4 (May 29, 2019); Stephen Ezell, *A New Frontier: Sustaining U.S. High-Performance Computing Leadership in an Exascale Era,* INFO. TECH. & INNOVATION FOUND. (Sept. 12, 2022), https://itif.org/publications/2022/09/12/high-performance-computing-leadership-in-an-exascale-era/ (accessed Jan. 24, 2024).

183 Hartung, *supra* note 182, at 6; Sarfaraz K. Niazi and Zamara Mariam, *Computer-Aided Drug Design and Drug Discovery: A Prospective Analysis*, PHARMS. at 5 (Dec. 22, 2023), https://www.mdpi.com/1424-8247/17/1/22 (accessed Feb. 11, 2021).

184 Zia Sadique et al., *A Machine-Learning Approach for Estimating Subgroup- and Individual-Level Treatment Effects: An Illustration Using the 65 Trial,* 42 MED. DECISION MAKING 923, 924 (Oct. 2022).

185 *See id.* at 925 (illustrating that factors such as variations in age can be tested using computer models).

186 Elisa Passini et al., *Why Computer Simulations Should Replace Animal Testing for Heart Drugs* THE CONVERSATION. (Mar. 26, 2018, 9:39 AM), https://theconversation.com/why-computer-simulations-should-replace-animal-testing-for-heart-drugs-93409 (accessed Jan. 25, 2024).

187 Elisa Passini et al., *Human In Silico Drug Trials Demonstrate Higher Accuracy than Animal Models in Predicting Clinical Pro-Arrhythmic Cardiotoxicity*, FRONTIERS PHYSIOLOGY at 11 (Sept. 12, 2017).

the Animal Welfare Act, research facilities must report annually to the Animal and Plant Health Inspection Service regarding, inter alia:[188]

- The number and species of animals used in tests, including the amount used in research with no pain, with pain, and with pain but without pain relief;
- The number and species of animals upon which tests were conducted involving pain or distress and for which the use of pain relief would have adversely affected the procedures, results, or interpretation of the teaching, research, experiments, surgery, or tests. As well, an explanation of the procedures producing pain or distress and the reasons pain relief was not used;
- Assurance that each principal investigator considered alternatives to painful procedures used on animals; and
- Assurance that professionally acceptable standards governing the care, treatment, and use of animals, including appropriate use of anesthetic, analgesic, and tranquilizing drugs, prior to, during, and following actual research, teaching, testing, surgery, or experimentation were followed by the research facility.[189]

C. CRAFTING A BETTER, HUMAN-CENTERED PROCESS

The drug development industry is under immense pressure from numerous fronts. Of primary importance among those pressures are: whether novel drug treatments can be discovered, how much drug development will cost, whether treatments shown to be safe in nonclinical tests will be shown as safe in clinical tests, whether treatments shown to be effective in nonclinical tests will show equal promise in clinical tests, and how long research testing will take. The utilization and continued development of human-centered testing would do much to ameliorate these pressures.

Animal-based testing, the historical system, is inherently slow and expensive for screening drugs meant for humans. An animal-based preclinical testing phase can last for three to six years alone.[190] One-third of drugs fail during the first clinical phase, and about half of drugs that end up entering clinical trials fail because of unforeseen toxicity in humans.[191] Another quarter of drugs fail in clinical trials because they are ineffective in having the desired effect.[192]

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188 9 C.F.R.§ 2.36.

189 9 C.F.R. § 2.36(b)(1).

190 Gregory Nierode et al., *supra* note 10, at 213.

191 *Id.*

192 *Id.*

Animal-based testing is a primary reason the cost of launching a new drug on the market exceeds $2.8 billion.[193] But, with efficient human-centered drug screening completed before expensive clinical trials, the cost and duration of new drug development can be dramatically decreased.[194] Although utilizing animals allows for systemic *in vivo* testing, the differences between human and non-human physiology do not allow for complete prediction of toxicity, potential side effects, and treatment efficiency in humans.[195] Moreover, animal testing is notably labor-intensive, protracted, and expensive.[196]

That is why the FDA Modernization Act 2.0 is such an important change to drug testing. Under the Act, researchers can complete preclinical testing solely focused on human physiology and human drug interactions, thus avoiding the pitfalls of animal-based testing.

D. PROPOSING THE FDA MODERNIZATION ACT 3.0

Even without a requirement that new drugs be tested on animals, the new drug approval process can be improved by further reducing reliance on animal testing. That improvement is based upon the premise that approval for human drugs should be human-centered. These improvements, styled as the FDA Modernization Act 3.0, include two elements: (1) the prohibition of animal testing where appropriate alternatives exist; and (2) the requirement that research facilities annually report their use of human-centered testing to the Food and Drug Administration.[197]

i. Favoring Human-Centered Nonclinical Testing

The first improvement is to prioritize human-centered testing. Simply put, human drug testing should utilize human physiology to ensure that drugs are safe and effective in humans. Animal testing informs researchers of outcomes in animals. As previously shown, extrapolating those outcomes to humans has caused many deaths and expensive delays, and also led to missed opportunities.

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193 Yanping Wang et al., *Emerging Trends in Organ-on-a-Chip Systems for Drug Screening*, 13 ACTA PHARMACEUTICA SINICA B 2483, at 2484 (June 2023); *see* Sebastian Rowe, *Modern Drug Discovery: Why is the Drug Development Pipeline Full of Expensive Failures?*, HARVARD UNIV.: SCI. NEWS (Apr. 21, 2020), https://sitn.hms.harvard.edu/flash/2020/modern-drug-discovery-why-is-the-drug-development-pipeline-full-of-expensive-failures/ (accessed Feb. 11, 2024) (discussing the role animal testing plays in the cost of drug development).

194 *Id.*

195 *Id.*

196 *Id.*

197 Although the proposals could amend the Animal Welfare Act, they are more aptly placed within the Federal Food, Drug, and Cosmetic Act because as animal testing is phased out, the Animal Welfare Act will become more and more irrelevant to new drug development laws.

Favoring human-centered testing will be accomplished by prohibiting animal testing where appropriate alternatives exist. An "appropriate alternative" is one that provides information of equivalent or better scientific quality and relevance compared to traditional animal testing methods.

To determine what alternatives meet this standard, the Food and Drug Administration should utilize an already-existing external validation agency such as the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). The ICCVAM is a permanent committee of the National Institute of Environmental Health Sciences.[198] Among other goals, it promotes the development, regulatory acceptance, and use of alternatives to animal testing.[199]

ii. Human-Centered Testing Reporting Requirements

In addition to the already-existing Animal Welfare Act reporting requirements, the Federal Food, Drug, and Cosmetic Act should require that researchers annually report to the Food and Drug Administration what human-centered alternatives researchers considered, what literature they reviewed to locate such alternatives, and, when applicable, specific reasons why no alternative satisfied their needs. Upon submission, the Administration would review for accuracy and completeness. If the Administration finds that a human-centered alternative was available, the researcher will be required to go back and repeat testing with an alternative. This will guarantee that human physiology is appropriately studied, and accordingly that drugs are safe and effective for humans.

When locating alternatives, in addition to their own literature review, researchers can refer to the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicology Methods (NICEATM) compiled list of alternatives already accepted by United States agencies.[200]

Additionally, these Animal Welfare Act annual reports will be made publicly available through posting on the Food and Drug Administration website. This will ensure that the public is dually made aware of the safety measures utilized for drug testing and the role animals are playing in those testing procedures. To ensure that researchers' confidential or proprietary testing methods are not released to competitors, researchers may propose redactions for publicly posted annual reports.

198 *About ICCVAM*, Nat'l Toxicology Program, https://ntp.niehs.nih.gov/whatwestudy/niceatm/iccvam (accessed Jan. 21, 2024).

199 *Id.*

200 *Alternative Methods Accepted by US Agencies*, Nat'l Toxicology Program, https://ntp.niehs.nih.gov/whatwestudy/niceatm/accept-methods (accessed Jan. 21, 2024).

E. ADDRESSING OPPOSITION TO ENDING ANIMAL TESTING

Some researchers believe that animal testing is necessary.[201] They believe that it is essential to advance biomedical research.[202] But, this entrenched support for animal testing is not due to necessity.[203] Instead, it is related to: (1) lack of research and education regarding human-centered alternatives; (2) researchers' adherence to familiar methods; and (3) researchers' reliance on historical data of animal models from times when alternatives were not available. For example, a 2020 study regarding testing on dogs within the Department of Veterans Affairs showed that many investigators cite their experience testing on dogs—and the historical data available in dog models—as justification to continue testing on dogs.[204] Even the study itself found that "these justifications are insufficient alone and constitute a form of circular reasoning that perpetuates the use of laboratory dogs without adequate examination of alternatives."[205]

Such justifications for continued animal testing make it clear that more education and experience are necessary to show some researchers that human models are just as good as, and maybe even better than, animal models. And, importantly, that animal models should not be considered the default.

IV. CONCLUSION

While no longer requiring animal testing is a stride forward, the FDA Modernization Act 2.0 has not gone far enough to ensure human safety. In spite of the changes the Act introduced, animal testing is still authorized and widely accepted. A human-centered approach is needed to enhance new drug safety and efficacy. It would also result in a quicker, less expensive system that allows patients to get the drugs that they need sooner.

The FDA Modernization Act 3.0 would ensure the highest level of human safety by making drug development human centered. That act would favor human-centered nonclinical testing by prohibiting animal testing where appropriate alternatives exist and by adding a reporting requirement for researchers' efforts to utilize human-centered testing.

This Article has revealed the challenges associated with animal-based testing by emphasizing the inherent dangers they pose to human

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201 *See e.g.* Francesca Petetta & Robert Ciccocioppo, *Public Perception of Laboratory Animal Testing: Historical, Philosophical, and Ethical View*, ADDICT BIOLOGY at 8–9 (Nov. 2021) (saying that animal testing is necessary if it is the only way to improve people's conditions or save lives).

202 *Id.* at 9.

203 *E.g.* Akhtar, *supra* note 111 (showing that animal testing results in poor predictive value); Norman, *supra* note 6 (explaining that animal toxicity testing often fails).

204 NAT'L ACADS. OF SCIS., ENG'G., AND MED., NECESSITY, USE, AND CARE OF LABORATORY DOGS AT THE U.S. DEPARTMENT OF VETERAN AFFAIRS (2020).

205 *Id.*

safety, the exorbitant costs they incur, and the unjustifiable delays they introduce to the development of new drugs. Standing at the crossroads of scientific advancement and historical entrenchment, it is imperative to commit to human-centered testing. By embracing cutting-edge technologies that align with both scientific progress and ethical imperatives, it will pave the way for safer and more cost-effective drug development.