



# BROKEN BUREAUCRACY

How **FDA Red Tape** punishes industry by  
forcing drug makers to kill puppies...  
and how cutting it expedited COVID-19 vaccines.







**BROKEN BUREAUCRACY** is a first-of-its-kind analysis of new drug applications (NDA) submitted to the Food & Drug Administration (FDA) from 2000-2020. These NDAs show what **FDA FORCES** industry to do to dogs and puppies for regulatory approval — even when drug makers oppose the FDA's outdated mandate.

**192** new drug applications analyzed

**808** toxicity tests analyzed.

Puppies as young as **1 WEEK OLD**. Most were **UNDER 1 YEAR** old.

As many as **20,000** puppies and dogs **PER YEAR** are abused and killed just to satisfy **FDA RED TAPE** and other government mandates.

That's potentially **1/3 OF ALL DOGS** abused in U.S. labs.

99% are **BEAGLES**.

The federal government says "beagles have become the breed of choice, due to their useful size and docile temperament."

An additional study was conducted on beagle dogs to examine the potential safety issue of buprenorphine patches if accidentally chewed with subsequent buccal absorption of buprenorphine. Buprenorphine patches (5 mg and 20 mg) were applied to the buccal areas of female beagle dogs and left in place for 30 min by taping close the mouths of the animals. 30 min, the patches were removed. Results showed decreased activity and red and swollen cheek mucosal areas in high dose groups within a few hours after dosing. No microscopic lesions were observed in any section of the buccal membrane from any dog, although red and swollen cheeks were noted grossly. Toxicokinetic data showed that buprenorphine was well absorbed after buccal administration in dogs given patches with holes. In this group, the mean Cmax within 30

Many suffered **PARALYSIS, BLINDNESS, CONVULSIONS**, and **BEAGLE PAIN SYNDROME**. Dogs died from "**HUMAN ERROR**," including **TRAUMA** during **FORCE FEEDING**, or incorrect dosing.

# 1938

Year when Congress passed the Food, Drug & Cosmetics Act. The FDA mandate is over 80 years old.

Given this context, and the substantial body of scientific literature indicating that nine-month dog **Vanda does not believe it should have to euthanize dozens of dogs** does not believe it should have to euthanize dozens of dogs in an unnecessary, unethical nine-month toxicity study before moving on to studying tradipitant in humans for longer than 12 weeks' duration. The **FDA disagrees** the multiple communications between Vanda and the FDA, including teleconferences, a request for formal dispute resolution, communications with the Director of the FDA's Center for Drug Evaluation and Research (CDER) and the Director of CDER's Office of New Drug **FDA insists** that Vanda must conduct an additional 9-month non-rodent toxicity study, not because the FDA has any tradipitant-specific safety concerns that need to be further explored in the additional study, but rather because it has adopted a non-binding guidance document says **"requires"** Vanda conduct the study.

Open letter  
from Vanda  
Pharmaceuticals  
to the FDA  
2/5/2019

It is clear after months of discussions with the FDA that the agency's opinion is immutable and that it views the guidance document's recommendation of nine-month non-rodent toxicity study as a binding requirement. For this reason **Vanda refused to do a nine-month dog study**

**95%**  
of drugs that pass  
FDA-mandated  
animal tests  
**FAIL**  
in humans.

**26%**  
Estimated R&D cost-savings  
for drug makers when allowed  
to utilize more efficient non-animal  
testing tools.

## \$900,000

Estimated cost of FDA-mandated test to  
force feed puppies tradipitant every day  
for **9 months** and kill them.

Vanda objected and was punished.  
Its stock value **crashed 20%.**

**60%** of taxpayers want to  
**Cut FDA Red Tape**  
after learning that Pfizer  
and Moderna's COVID-19  
vaccines were rapidly developed  
and fast-tracked through FDA's  
normal animal-testing mandate.

## Report Highlights

- A first-of-its-kind analysis by White Coat Waste Project documents how thousands of puppies are abused in wasteful, misleading, and expensive drug tests just to satisfy archaic FDA red tape. For this report, WCW reviewed new drug applications (NDAs) submitted to the Food and Drug Administration (FDA) by pharmaceutical companies over the last 20 years.
- These NDAs are important because they describe, in industry's own words, what pharmaceutical companies are forced to do to dogs for regulatory approval.
- As many as 20,000 puppies and dogs a year are abused and killed for no reason other than to satisfy FDA red tape and other government mandates. That's potentially one third of *all* dogs used in U.S. labs.
- The nearly 200 drug applications analyzed by WCW describe how over 11,000 puppies and dogs were subjected to FDA-mandated tests.
- Puppies abused in FDA-mandated drug screening tests were as young as one week old, and most were under a year old.
- Puppies were forced to inhale experimental drugs by having masks strapped to their faces, or made to ingest drugs by having tubes forced down their throats. Some had their mouths taped shut to prevent them from spitting out the experimental drugs. Dogs were reported to "vocalize" and "struggle" during dosings, indicating pain.
- Many dogs suffered adverse effects like foaming at the mouth, becoming comatose or paralyzed, blindness, convulsions, idiopathic febrile necrotizing arteritis syndrome (otherwise known as "beagle pain syndrome"), and more. In many of the FDA-mandated studies, dogs were reported as having been "found dead" or dying from "human error," including trauma during force-feeding, or incorrect dosing.
- Even though more efficient and effective test methods exist, the FDA continues to force drug companies to waste millions of dollars, years of time, and countless dogs' lives on wasteful animal tests.
- Companies that have challenged the FDA's dog testing red tape have been rejected and punished, hindering the development of potential drugs for COVID-19 and other illnesses.
- The COVID-19 pandemic has demonstrated that safe and effective drugs can be developed and brought to human trials without needless FDA dog testing red tape.
- The government's own findings show more than 95 percent of drugs that pass FDA-mandated animal tests fail in humans, because they are found to be ineffective or dangerous, resulting in billions in wasted money and decades of lost time.
- Polling shows a supermajority of taxpayers from both parties say the FDA should abolish its dog testing mandate. Congress has responded with bipartisan efforts at regulatory reform.



## Executive Summary

**The Food and Drug Administration's approval process for new medicines and vaccines is broken, and federal bureaucracy is to blame. The solution is regulatory relief: cut FDA red tape to spare dogs, stop waste, spur innovation, and save lives.**

A first-of-its-kind White Coat Waste Project analysis of drug applications submitted to the Food and Drug Administration (FDA) by pharmaceutical companies over the last 20 years documents how thousands of puppies are abused in wasteful, misleading, and expensive drug tests just to fulfill an archaic bureaucratic government mandate.

Some of the puppies were just one week old. Practically none had even reached their first birthday. They had experimental drugs forced down their throats and into their stomachs for as long as a year. Some dogs had their mouths taped shut so they couldn't throw up the experimental drugs they were force-fed. Sometimes they were dosed via an injection directly into their eyes and were then killed and dissected by pharmaceutical manufacturers, for just one reason: FDA red tape.

### 2) **39-Week Oral Gavage Chronic Toxicity and Toxicokinetic Study with** **KO5185426-006 in Dogs with an 8-Week Recovery Phase**

This study was intended to continue for 39 weeks but the high g/kg BID PO proved intolerable after 10 days and animals and examined. These dogs were replaced on study and dosing was resumed on day 19 at a lowered dose of 300 mg/kg BID PO in the HD dogs. This dose also proved intolerable and dosing was again suspended on day 37. The study was aborted and the dogs transferred to the subsequent 13 week study (*vide infra*, study1032862).

The HD dogs showed clinical signs of excessive salivation, vomiting, dehydration, soft or malformed feces and hyperactivity. MD (150 mg/kg BID) animals showed dogs in all dosed groups vocalized and struggled during dosing suggesting pain. HD animals, particularly those k of thin appearance, tremor and reddened skin.

The nearly 200 drug applications analyzed by WCW for this report describe how at least 11,443 puppies and dogs were subjected to tests where most suffered adverse effects like foaming at the mouth, becoming comatose or paralyzed, losing their sight or their hair, gasping for breath, pneumonia, bleeding in their hearts, depression, convulsions, and more. In many of the FDA-mandated studies, dogs were reported as having been "found dead" or dying from "human error," including trauma during force-feeding, or incorrect dosing.

Beyond the horror of what these puppies are subjected to, the consequences of the FDA requiring drugs to be tested on dogs are dire. Safe and effective drugs are discarded based on false negative results from misleading animal tests required by the

FDA. Likewise, dangerous and ineffective drugs make it to human trials after “passing” false positive tests on dogs.

Over 95 percent of drugs that pass these government-mandated animal tests fail in humans.<sup>1</sup> As a result, businesses waste billions on failed drugs and innovation is stifled. Consumers and patients wait longer for cures, and medical costs skyrocket. Drug companies that have attempted to avoid these wasteful tests have been rejected and punished.<sup>2</sup>

For all these reasons, taxpayers want reform as much as they need it, with a supermajority from both parties saying the FDA should abolish its dog testing mandate. Bipartisan lawmakers have also demanded the FDA take action. The calls grow louder, as the failure of animal testing has become clearer while emerging technologies provide more and better alternatives to testing on dogs.

The urgent need to develop COVID-19 vaccines and therapeutics has underscored the importance—and viability—of this initiative to eliminate the FDA’s counterproductive dog testing red tape. Under these extraordinary circumstances, the drug maker Moderna has successfully developed and gained approval for a safe and highly effective COVID-19 vaccine without conducting animal testing prior to human clinical trials, with the FDA’s blessing.

An additional study was conducted on beagle dogs to examine the potential safety issue of buprenorphine patches if accidentally chewed with subsequent buccal absorption of buprenorphine. Buprenorphine patches (5 mg and 20 mg) were applied to the buccal areas of **female beagle dogs and left in place for 30 min by taping close the mouths of the animals.** 30 min, the patches were removed. Results showed decreased activity and red and swollen cheek mucosal areas in high dose groups within a few hours after dosing. No microscopic lesions were observed in any section of the buccal membrane from any dog, although **red and swollen cheeks were noted grossly.** Toxicokinetic data showed that buprenorphine was well absorbed after buccal administration in dogs given patches with holes. In this group, the mean C<sub>max</sub> within 30 min was 174 ng/ml and the mean AUC was 245±242 ng/ml/hr. The apparent t<sub>1/2</sub> was 2.5 hours. These results indicate that accidental buccal absorption may be a potentially significant safety issue, particularly if children were to chew used (discarded) or unused patches.

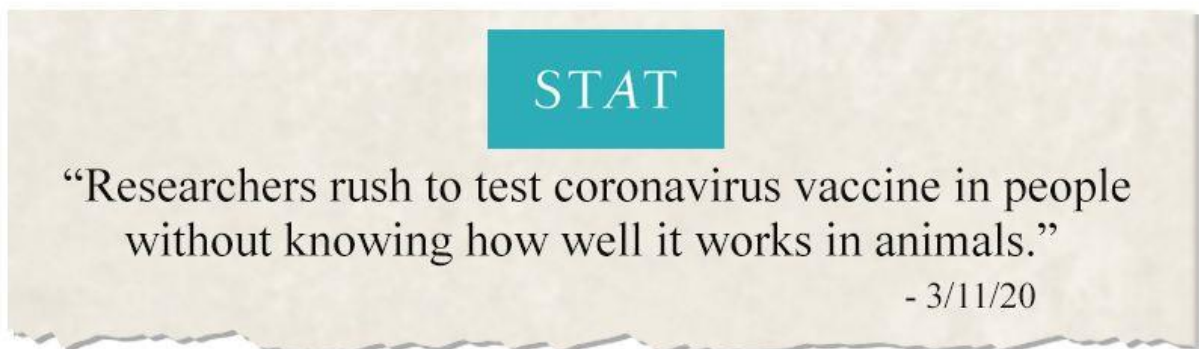
<sup>1</sup> Attila A. Seyhan (November 18, 2019), “Lost in translation: the valley of death across preclinical and clinical divide – identification of problems and overcoming obstacles,” Translational Medicine Communications 4, 18. <https://doi.org/10.1186/s41231-019-0050-7> (accessed on December 22, 2020)

<sup>2</sup> Vanda Pharmaceuticals, “Open Letter to the Food and Drug Administration, Vanda Pharmaceuticals Takes a Stand Against Unnecessary Animal Research,” February 5, 2019, [https://mma.prnewswire.com/media/818251/Open\\_Letter.pdf](https://mma.prnewswire.com/media/818251/Open_Letter.pdf) (accessed on December 10, 2020)

While the FDA has taken some promising steps in the right direction, **this urgent problem needs more immediate and concrete action. White Coat Waste Project recommends:**

- **Audit the FDA:** The Government Accountability Office should audit the FDA to determine the extent to which the FDA has—or has not—allowed companies to use alternatives to dog tests, what metrics the agency uses to assess the effectiveness of its programs to curb mandated testing on dogs, and what improvements can be made to reduce wasteful dog tests.
- **Enact the AARF ACT:** Congress should pass the bipartisan Alternatives to Animals for Regulatory Fairness Act (H.R. 1905 in the 117<sup>th</sup> Congress)—known as the AARF Act—to codify drug companies' freedom to avoid the FDA's dog testing mandate and utilize more productive testing methods.
- **Modernize regulations and guidances:** The FDA should revise its current regulations and issue detailed guidance on how drug makers can avoid testing on dogs under the current legal framework.
- **Enhance accountability:** The FDA's Alternative Methods Working Group should establish key performance indicators and timelines for its efforts to expand regulatory acceptance of non-dog testing methods.

**The federal government must cut FDA red tape to get treatments to market faster, cheaper, with fewer dead dogs, and without delay.**





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## History of the FDA's Dog Testing Mandate

The FDA's dog testing mandate began in tragedy eight decades ago—and persists today despite causing real harm to patients, drug makers, and dogs.

In 1937, more than 100 people, many of them children, died after taking an unsafe drug called Elixir Sulfanilamide—the manufacturer had released a new formulation of the antibiotic, which was raspberry flavored and, it was discovered, extremely deadly.<sup>3</sup>

Congress responded with the Food, Drug, and Cosmetic Act, signed into law by President Franklin Roosevelt on June 25, 1938, mandating drugs be proven safe to be marketed to American consumers. Since 1955, various amendments to the Food, Drug, and Cosmetic Act and industry guidance documents have been issued by the FDA directing drug makers to use dogs in the testing process.<sup>4</sup>

### Guidance for Industry, Investigators, and Reviewers

U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)

Before the human studies can begin, an IND must be submitted to the Agency containing, among other things, information on any risks anticipated based on the results of pharmacologic and toxicological data collected during studies of the drug in animals (21 CFR 312.23(a)(8)). These basic safety tests are most often performed in rats and dogs.

**tests are most often performed in rats and dogs.**

The FDA's guidance documents are not binding law.  
There is no legal basis for the FDA's dog testing mandate.  
It could be reversed at any time.

Animal testing—including the FDA's required dog testing for drugs—remains part of that process today, under the outdated and debunked notion that beagles and humans are physiologically similar enough that testing on one could provide actionable information about the other.<sup>5</sup>

<sup>3</sup> Carol Ballentine, "Taste of Raspberries, Taste of Death: The 1937 Elixir Sulfanilamide Incident," FDA Consumer Magazine, June 1981, <https://www.fda.gov/files/about%20fda/published/The-Sulfanilamide-Disaster.pdf> (accessed on December 10, 2020)

<sup>4</sup> A. C. Jacobs, K. P. Hatfield (March 2013), "History of Chronic Toxicity and Animal Carcinogenicity Studies for Pharmaceuticals," Vet Pathol; 50(2):324-33. doi: 10.1177/0300985812450727

<sup>5</sup> Ray Greek, Niall Shanks, Mark J Rice (October 2011), "The History and Implications of Testing Thalidomide on Animals," The Journal of Philosophy, Science & Law 11(3) DOI: 10.5840/jpsl20111133

A 2020 paper co-authored by the FDA, other federal agencies, and industry clearly documents that dogs are still the main non-rodent species used in FDA-mandated drug tests.<sup>6</sup> One FDA industry guidance document on how to apply for approval to test an investigational new drug (IND) on humans states:<sup>7</sup>

*“Before the human studies can begin, an IND must be submitted to the Agency containing, among other things, information on any risks anticipated based on the results of pharmacologic and toxicological data collected during studies of the drug in animals (21 CFR 312.23(a)(8)). **These basic safety tests are most often performed in rats and dogs.**”*

Despite the FDA treating them as if they are, these guidance documents are not, however, binding law. In fact, there is no legal basis for the dog testing mandate.

While the Food, Drug, and Cosmetic Act continues to state that human and animal data only must be the basis for new drug applications, FDA guidance—though still prioritizing dog use—does open the door to the use of non-dog testing tools instead.

The FDA’s 2010 non-binding international industry guidance document that the agency treats as a regulation to guide drug development states, “You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations.”<sup>8</sup> This international guidance that the FDA relies on further states, “alternative approaches not described in this guidance can also be used....It is recommended that these alternative approaches be discussed and agreed upon with the appropriate regulatory authority. The use of any of these approaches can reduce overall animal use in drug development.”

Unfortunately, U.S. law has not been amended to reflect this and the FDA has not issued instructions or regulations outlining a process for how drug makers can avoid animal tests. In many cases the FDA puts up roadblocks to the regulatory use and acceptance of these tools, commonly rejecting attempts by companies to use alternatives and even forcing them to conduct dog testing they do not want or need to get safe and effective drugs into human trials.

Indeed, as is discussed in more detail in subsequent sections, the regulations have been slow to catch up to the science.

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<sup>6</sup> Helen Prior et al. (June 2020), “Opportunities for use of one species for longer-term toxicology testing during drug development: A cross-industry evaluation,” *Regulatory Toxicology and Pharmacology*, Volume 113, 2020, 104624, ISSN 0273-2300, <https://doi.org/10.1016/j.yrtph.2020.104624>, <http://www.sciencedirect.com/science/article/pii/S0273230020300507> (accessed on December 22, 2020)

<sup>7</sup> Food and Drug Administration, “Guidance for Industry, Investigators, and Reviewers Exploratory IND Studies,” FDA website, 2006, <https://www.fda.gov/files/Guidance-to-Industry-and-Reviewers---Exploratory-IND-Studies-%28PDF%29.pdf> (accessed on December 10, 2020)

<sup>8</sup> Food and Drug Administration, “Guidance for Industry M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals,” FDA website, January 2010, <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/m3r2-nonclinical-safety-studies-conduct-human-clinical-trials-and-marketing-authorization> (accessed on December 10, 2020)

A U.S. government report published in 1986 stated, “[Animal tests] are used in part because investigators believe that Federal regulatory agencies, such as FDA and EPA, require the results of these tests in data submissions....Exercise of oversight authority could induce Federal regulatory agencies to make explicit their disinterest in data derived from objectionable tests and to demonstrate their ready acceptance of data obtained through alternate means.”<sup>9</sup> The report details how the FDA’s strong emphasis on animal testing in guidance documents led companies to believe it was required even in cases where it wasn’t. Sadly, this has not improved even 35 years later.

### 6.2.3 Repeat Dose Studies in the Dog

**Study title: 14-Day Dose-Range-Finding Study in Dogs and Monkeys; Oral Administration (Study no. CD01/7766T, GLP)**

A multiple ascending-dose study was carried out in a single **beagle dog** and Cynomolgus monkeys to determine appropriate doses for the nonrodent repeat dose toxicity studies. In the dog, Diltiazem was administered once daily at 15, 30 and 60 mg/kg by **Oral gavage** and mid dose were administered each for 7 days. The high dose was only administered for 1 day. At the high dose of 60 mg/kg/day, the single animal was euthanized due to excessive clinical signs including clonic and tonic convulsions, inability to stand, ataxia and head swaying. Clinical signs first appeared 17 min after dosing. By 2.5 h after dosing, some clinical signs remained including slight **ataxia, head movements and tremors. Emesis** 30 mg/kg/day, excitement and rigidity was noted 1 h post-dose and resolved by 2.5 h post-dose. A single monkey was administered 15, 30, 60 and 80 mg/kg once daily by oral gavage. The first 3 dose levels were administered for 7 days each and the high dose of 80 mg/kg was administered for 4 days. At the high dose, the animal was euthanized after 4 days of dosing due to clonic convulsions. Emesis occurred after each of the 4 doses of 80 mg/kg. No effects on body weight were evident and the only drug related changes noted were increased heart, liver and adrenal gland weights and microscopic findings in the gastric mucosa. A group of 3 monkeys were then administered 40 mg/kg/day for 29 days. At this dose, emesis and tremors occurred in all animals. A single female monkey had 2 instances of clonic convulsions (Day 6 and 24) and sporadic motor incoordination. A separate female had a single instance of slight head movements. Other drug related effects included a decrease in erythrocyte, hemoglobin and hematocrit levels and slightly increased serum glucose and ALT/GOT levels. Increased adrenal weights were noted in a single female. The monkey was selected as the non-rodent species for

Even today, the FDA provides extensive guidance on how to use dogs in testing, and virtually none on how companies can use alternatives instead.<sup>10</sup>

The dog tests currently required by the FDA are the same as they were in 1997,<sup>11</sup> while the government’s own experts acknowledge they are not reliable for their intended purpose and better alternatives exist. That’s why the Environmental Protection Agency

<sup>9</sup> U.S. Congress, Office of Technology Assessment: Alternatives to animal use in research, testing, and education. U.S. Government Printing Office, OTA-BA-273, Washington, DC, 1986.

<sup>10</sup> Food and Drug Administration, “General Considerations for Animal Studies for Cardiovascular Devices - Guidance for Industry and FDA Staff,” FDA website, July 2010, <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/general-considerations-animal-studies-cardiovascular-devices-guidance-industry-and-fda-staff> (accessed on December 10, 2020)

<sup>11</sup> Vanda Pharmaceuticals, “Open Letter to the Food and Drug Administration, Vanda Pharmaceuticals Takes a Stand Against Unnecessary Animal Research”



(EPA) phased out its blanket requirement to conduct long-term dog toxicity studies beginning in 2007,<sup>12</sup> and in 2019 committed to ending all testing on mammals by 2035.<sup>13</sup>

The FDA's outdated dog testing regulation is over 80 years old and 1930s science no longer serves our public health needs. In fact, the FDA's red tape leads to adverse, unintended consequences for public health, puppies, and the economy—causing rather than alleviating harm.

This FDA regulation started out with tragedy and good intentions. But with so much at stake, the treatment can't be worse than the disease.

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<sup>12</sup> Environmental Protection Agency, Pesticides; Data Requirements for Conventional Chemicals; Final rule, Federal Register (72 FR 60934, October 26, 2007) (FRL-8106-5)

<sup>13</sup> David Grimm, "U.S. EPA to eliminate all mammal testing by 2035," Science, September 10, 2019, <https://www.sciencemag.org/news/2019/09/us-epa-eliminate-all-mammal-testing-2035> (accessed on December 11, 2020)

## Polling Shows Overwhelming Support for Reform

Regulatory reform is not just sound science but is also what taxpayers—Republicans and Democrats alike—say they want, as well. That is, once they learn of the FDA’s requirement that drug companies test on dogs in maximum pain experiments.

Awareness of this requirement is low. Polling shows most taxpayers—68 percent—do not know about the FDA’s dog testing mandate.<sup>14</sup> However, of those who are aware, just about two-thirds say they want to cut FDA red tape. This includes 73 percent of Republicans and 66 percent of Democrats.<sup>15</sup>

These national polls of 1,000 taxpayers were conducted by Lincoln Park Strategies in May and June 2020. Further polling conducted since then shows a continued robust support for change.

A national poll of over 1,000 taxpayers conducted by Lincoln Park Strategies just ahead of the 2020 election found 62 percent of Republicans and 54 percent of Democrats wanted the next president to end the FDA’s requirement that drugs be tested on dogs.<sup>16</sup>

Furthermore, 60 percent of taxpayers—including 57 percent of Republicans and 67 percent of Democrats—want to cut FDA red tape upon learning that Pfizer and Moderna Therapeutics’ COVID-19 vaccines were allowed to bypass animal testing prior to human trials.<sup>17</sup>

It’s not just polling showing taxpayers’ preference for change. As of February 2021, more than 117,000 taxpayers of all political stripes have signed White Coat Waste Project’s online petition calling for the FDA to change its rules and allow drug companies to pursue superior alternatives to mandated dog testing.<sup>18</sup>

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<sup>14</sup> Lincoln Park Strategies, National Omnibus Poll, June 2020

<sup>15</sup> Lincoln Park Strategies, National Omnibus Poll, May 2020

<sup>16</sup> Lincoln Park Strategies, National Omnibus Poll, September 2020

<sup>17</sup> Lincoln Park Strategies, National Omnibus Poll, January 2021

<sup>18</sup> White Coat Waste Project, “#CutFDARedTape: Abolish Cruel, Wasteful FDA Dog Testing Requirements!” 2020, <https://www.change.org/p/food-and-drug-administration-cutfdaredtape-abolish-cruel-wasteful-fda-dog-testing-requirements> (accessed on December 24, 2020)

## WCW Analysis of Dog Tests Included in FDA Drug Applications

In an effort to determine the scale and impact of the FDA's dog testing mandate, White Coat Waste Project performed a first-of-its-kind analysis of New Drug Applications (NDAs) available on the FDA website.

NDAs are comprehensive applications describing the history of a drug's development and testing, that are used by pharmaceutical manufacturers to propose new drugs be approved by the agency for marketing to American consumers. These NDAs were submitted to the FDA between the years of 2000 and 2020.

WCW identified and reviewed 192 complete NDAs for human drug trials, including results from 808 toxicity tests on dogs, involving at least 11,443 puppies. This sample gives an important look into what government regulators are forcing drug companies to do to thousands of puppies every single year.



These are just some of the grim details WCW uncovered. What follows is an examination of the sampled NDAs, and what they reveal about how the FDA's dog testing mandate is applied to the puppies victimized by the agency's bureaucratic whims.

### Method

Using the FDA website, we compiled 192 complete NDAs for human drugs that included results from toxicity tests on dogs.<sup>19</sup> This convenience sample included NDAs submitted by 17 different drug companies between 2000 and 2020.

### Results

#### Number of dog studies and dogs used

The 192 NDAs reviewed reported a total of 808 dog studies that used at least 11,443 dogs.

#### Dog characteristics

##### *Breeds*

Ninety-nine percent of the studies that listed breed used beagles.<sup>20</sup> According to a federal government website, "beagles have become the breed of choice, due to their useful size and docile temperament."<sup>21</sup>

<sup>19</sup> Applications that only referenced previously published dog studies—and did not include new data—were excluded.  
<sup>20</sup> 196 of the 808 studies did not have breed listed.

<sup>21</sup> U.S. Department of Health and Human Services Office of Research Integrity. (2004). Dogs. Retrieved November 5, 2016, from Office of Research Integrity, <http://ori.hhs.gov/education/products/ncstate/dog.htm>



### *Age*

Ninety percent of NDAs that reported dog ages included at least some dogs who were 1 year old or younger.<sup>22</sup> Of the studies that listed age, the youngest dogs used were 7 days old and the oldest dogs used were 5 years old.

In one study, 32 7-day-old male and female beagle puppies were force-fed an experimental drug by oral gavage for 13 weeks. The NDA noted that the puppies experienced vomiting, retching, diarrhea, and other adverse effects.

### Dog study details

#### *Study duration*

The duration of the dog studies reviewed ranged from a single dose to one year long.<sup>23</sup>

#### **Most common dog study durations<sup>24</sup>**

<b>Duration</b>	<b>Number of Studies</b>
<b>Single Dose</b>	151
<b>4 weeks</b>	115
<b>13 weeks</b>	67
<b>2 weeks</b>	59
<b>39 weeks</b>	48
<b>1 year</b>	35
<b>1 week</b>	32
<b>26 weeks</b>	32
<b>1 day</b>	11
<b>5 days</b>	10

#### *Drug administration routes*

The most common drug administration route in the NDAs reviewed was force-feeding by oral gavage—a painful but common laboratory process, for which a tube is inserted into the dogs' mouths and through their bodies, so chemical compounds can be delivered directly into their stomachs.<sup>25</sup> Other common drug exposure methods included intravenous, inhalation, intramuscular injection, and others detailed below.

In one study, twelve beagles had their mouths taped shut, so they could not expel the experimental drugs they were forced to ingest. These dogs suffered “decreased activity”

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<sup>22</sup> 267 of 808 dog studies listed the animals' age.

<sup>23</sup> 158 studies did not have durations listed.

<sup>24</sup> Study durations included in at least 10 NDAs.

<sup>25</sup> 105 studies did not list drug routes.

and inflamed, swollen cheeks as a result of the pointless cruelty they endured at the behest of FDA bureaucrats.

**Most common drug exposure methods<sup>26</sup>**

Exposure route	Number of Studies
Oral gavage	409
IV	126
Oral/ IV	42
Inhalation	39
Intramuscular	18
Eye	14
Infusion	11

**Reported adverse effects in dogs**

- At least 88 studies involved premature and unplanned deaths where dogs found dead
- 10 dogs died due to human error, including trauma during force-feeding or incorrect dosing
- 123 of the 192 studies reviewed involved dogs who experienced vomiting and/or retching
  - 2,869 dogs were used in studies where dogs experienced vomiting and/or retching

Other adverse effects observed in dogs included:

- Foaming at the mouth
- Comatose
- Loss of sight
- Gasping for breath
- Massive bleeding in the heart
- Skin lesions and scabs
- Hair loss
- Severe dehydration
- Body and facial swelling
- Paralysis
- Convulsions, nervousness, body tremors, and trembling
- Depression
- Severe weight loss
- Bloody feces
- Pneumonia

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<sup>26</sup> Study durations included in at least 10 NDAs.

In one study WCW uncovered, 32 week-old puppies were force-fed an experimental drug by oral gavage for 13 weeks. Records show the 32 puppies experienced vomiting, retching, and diarrhea, and were then killed.

In a fourteen-week-long study for a drug to treat head lice, dozens of dogs were force-fed the drug and experienced tremors, dehydration, anorexia, loss of muscle control, and some became comatose and died. Others were killed because they became so ill.

One 9-month drug study was repeatedly suspended due to dogs dying from the high doses the experimenters were giving them. The surviving dogs were “recycled” into a 3-month study when the 9-month experiment was aborted.

“Some dogs in all dosed groups vocalized and struggled during dosing suggesting pain,” according to the records.

Another year-long drug study done on 43 beagles led to multiple dogs suffering idiopathic febrile necrotizing arteritis syndrome, otherwise known as “beagle pain syndrome.” One with that condition was euthanized after just one week. She was replaced in the study, with another dog.

The dogs in this study, and a second round of experiments on the same drug which used 24 beagles for 13 weeks, also suffered convulsions, body tremors, extreme anxiety, weak pulses, and high heart rate, in addition to one dog’s “premature euthanasia” due to fever complications.

Records note, without explanation, that at least one dog’s coat “was also markedly wet, ungroomed and covered in sawdust.”

Mortality					
According to the pathologist’s report, the mortalities of animals # 109, 114, and 118 were attributed to gavage trauma or dose administration errors					
findings possibly related to death/euthanization are listed in the table below. The mortalities could possibly be due to gavage or dose administration errors, however, it is not completely clear, especially for animal #114, the animal that was euthanized. The temporal relationship between the dosing and deaths or euthanization is not provided.					
Dose of PF-02341066	Animal #	Sex	Found Dead or Euthanized	Day	Important observations related to euthanization or death
250 mg/kg	109	Female	Found dead		<p><b>Left eye partially closed, haircoat stained on nose (red)</b></p> <p>pathology findings: inflammation in esophagus, thymus (crystal-like eosinophilic material mixed with inflammatory infiltrate on the thymic capsule)</p> <p><b>gavage trauma</b></p>
	111	Female	Found dead	21	<ul style="list-style-type: none"> <li>No clinical signs</li> <li>Gross pathology/ histopathology findings: abnormal color (red) and congestion in lung</li> </ul>
	114	Female	Euthanized	44	<ul style="list-style-type: none"> <li>Activity decreased, thorax edema, left eye partially closed, haircoat stained on nose (red)</li> <li>Gross pathology/ histopathology findings: Submucosal infiltration of brown pigment laden macrophages in esophagus, inflammation in trachea</li> </ul> <p><b>lame/limping</b></p>
	118	Female	Found dead	44	<ul style="list-style-type: none"> <li>Chromodacryorrhea</li> <li>Gross pathology/ histopathology findings: submucosal hemorrhage in esophagus, inflammation in trachea and lung, gavage trauma in thymus (crystal-like eosinophilic foreign material mixed with inflammatory infiltrate on the thymic capsule)</li> </ul>



## Criticism of the FDA's Dog Testing Mandate

The FDA's dog testing mandate is roundly criticized by scientists and policy experts as burdensome, overbroad, and unscientific, causing real harm to dogs, businesses, and patients.<sup>27</sup>

**The harms to dogs are obvious.** As described in the previous section, as many as 20,000 puppies and dogs a year are abused and killed for no reason other than to satisfy government mandates.<sup>28</sup>

**The requirement that drugs be tested on dogs is also harmful to businesses.** On average, it takes over 13 years and over \$2.6 billion to get a new drug from discovery to approval.<sup>29</sup> The significant cost and time can be attributed in part to multi-million-dollar, years-long animal testing that regulators require before a drug can be considered for human trials.

In an effort to reduce the time and expense associated with new drug development, pharmaceutical companies are increasingly adopting the use of non-animal drug screening tools. Indeed, the industry has increased research and development spending while also decreasing animal testing in recent years by choosing to integrate more efficient cutting-edge technologies like organs-on-chips and computer models.<sup>30</sup> Experts estimate that pharmaceutical R&D costs could be cut by as much as 26 percent by allowing drug companies to utilize more efficient non-animal testing tools.<sup>31</sup>

Yet, the FDA has refused to allow companies to fully employ these high-tech tools to fulfill regulatory requirements.

Because of this, companies waste years of time and billions of dollars on failed drugs, and abandon potentially useful ones, due to misleading FDA-mandated animal tests and the government's refusal to allow drug developers to rely on more accurate testing tools.

Abolishing regulations and policies that require animal use, meanwhile, "will benefit pharmaceutical industry stakeholders, including patients whose health depends on

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<sup>27</sup> Lisa A. Kramer, Ray Greek (March 7, 2018), "Human Stakeholders and the Use of Animals in Drug Development," *Business and Society Review*, Vol. 123, Issue 1, pp. 3-58

<sup>28</sup> In 2018, 65,788 total dogs were confined in U.S. laboratories. While the U.S. does not track animal use by purpose, data from Canada and Europe show that between 25 percent and 71 percent of dog use is for government-mandated testing. Hence, our estimate here that 20,000 of 65,788 dogs used in the U.S. are tested on to meet FDA requirements.

<sup>29</sup> Seyhan, "Lost in translation: the valley of death across preclinical and clinical divide – identification of problems and overcoming obstacles"

<sup>30</sup> "Animal Testing and Its Alternatives – the Most Important Omics Is Economics," 2018, *ALTEX - Alternatives to Animal Experimentation* 35 (3):275-305. <https://doi.org/10.14573/altex.1807041> (accessed on December 24, 2020)

<sup>31</sup> Nora Franzen et al. (September 2019), "Impact of organ-on-a-chip technology on pharmaceutical R&D costs," *Drug Discovery Today*, Volume 24, Issue 9, September 2019, Pages 1720-1724, <https://doi.org/10.1016/j.drudis.2019.06.003> (accessed on December 22, 2020)

drugs and the many people who rely on the financial well-being of pharmaceutical firms,” say experts.<sup>32</sup>

Given this context, and the substantial body of scientific literature indicating that nine-month dog **Vanda does not believe it should have to euthanize dozens of dogs** does not believe it should have to euthanize dozens of dogs in an unnecessary, unethical nine-month toxicity study before moving on to studying tradipitant in humans for longer than 12 weeks’ duration. The **FDA disagrees** the multiple communications between Vanda and the FDA, including teleconferences, a request for formal dispute resolution, communications with the Director of the FDA’s Center for Drug Evaluation and Research (CDER) and the Director of CDER’s Office of New Drug **FDA insists** that Vanda must conduct an additional 9-month non-rodent toxicity study, not because the FDA has any tradipitant-specific safety concerns that need to be further explored in the additional study, but rather because it has adopted a non-binding guidance document says **“requires”** Vanda conduct the study.

It is clear after months of discussions with the FDA that the agency’s opinion is immutable and that it views the guidance document’s recommendation of nine-month non-rodent toxicity study as a binding requirement. For this reason **Vanda refused to do a nine-month dog study**

Open letter from Vanda Pharmaceuticals to the FDA, 2/5/19

Yet with few exceptions, the FDA has refused to allow companies to use these high-tech tools to fulfill regulatory requirements and hasn’t been transparent about its procedures and criteria governing those exceptions.

This is a long-standing concern. In 2017, the U.S. Government Accountability Office (GAO)—the independent Congressional watchdog for all government agencies—released a report critical of the FDA for trying to force sunscreen companies to conduct unnecessary, expensive, and cruel tests on animals.<sup>33</sup> Among the problems the GAO identified, is that requiring this animal testing could make it difficult or even impossible for companies to do business in countries which prohibit testing sunscreen on animals, and could also provoke a backlash from consumers and shareholders.

A real-world example shows how these concerns about the dog testing mandate’s harms to businesses are not trivial, abstract, or merely academic propositions. The FDA’s refusal to allow alternatives to dog testing, and its lack of transparency, made Vanda Pharmaceuticals a victim of the FDA’s red tape.

This forward-looking company had successful human trials of a drug indefinitely suspended by the FDA because it refused to spend what the government itself

<sup>32</sup> Kramer, Greek “Human Stakeholders and the Use of Animals in Drug Development,” 4

<sup>33</sup> U.S. Government Accountability Office, “SUNSCREEN FDA Reviewed Applications for Additional Active Ingredients and Determined More Data Needed,” GAO website, November 2017, <https://www.gao.gov/assets/690/688390.pdf> (accessed on December 10, 2020)

estimates would be nearly \$900,000<sup>34</sup> to force-feed puppies the drug every day for nine months and then kill and dissect them.<sup>35</sup> This, after the company had already conducted limited animal testing to gain FDA approval for the clinical trials.

The FDA halted the trials—thereby forcing sick patients to stop taking the drug—even after Vanda provided the FDA with extensive evidence that the drug is safe and effective in humans and that the additional dog tests would not add any value.

One consequence of the FDA's decision is that Vanda's stock plummeted nearly 20 percent, costing the company and its shareholders tens of millions of dollars.<sup>36</sup> Even worse, the drug Vanda was developing, tradipitant, now shows promise as a COVID-19 treatment,<sup>37</sup> and might have been available for use in human trials earlier without the FDA's rigid and pointless adherence to its dog testing mandate.

"The animal studies the FDA demands...have been considered routine in the pharmaceutical industry for decades, despite the growing body of evidence discrediting such studies' scientific value," said Vanda Pharmaceuticals CEO Mihael Polymeropolous.<sup>38</sup>

**The dog testing mandate harms patients.** Drugs that are safe and effective may not reach those who need them because of animal testing's misleading false negative results. Perhaps even more alarmingly, thanks to false positive results, drugs that appear safe during animal testing are only later discovered as hazardous to human consumers.

FDA scientists recognize this problem, stating in a 2019 report that "the loss of opportunities in testing these false-positive drugs in human patients may present an even bigger problem not including drug candidates that were dropped from development before being tested in humans in the two databases."<sup>39</sup>

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<sup>34</sup> Environmental Protection Agency, "Cost Estimates of Studies Required for Pesticide Registration," July 2019, <https://www.epa.gov/pesticide-registration/cost-estimates-studies-required-pesticide-registration> (accessed on December 22, 2020)

<sup>35</sup> Vanda Pharmaceuticals, "Open Letter to the Food and Drug Administration, Vanda Pharmaceuticals Takes a Stand Against Unnecessary Animal Research"

<sup>36</sup> Ed Silverman, "Drug maker sues FDA over a dog study — and its stock goes into a tailspin," STAT, February 6, 2019, <https://www.statnews.com/pharmalot/2019/02/06/vanda-sues-fda-over-a-dog-study-and-its-stock-sinks/> (accessed on December 10, 2020)

<sup>37</sup> "Vanda's experimental COVID-19 drug shows promise in interim trial data," Reuters, August 18, 2020, <https://www.reuters.com/article/us-health-coronavirus-vanda-pharms/vandas-experimental-covid-19-drug-shows-promise-in-interim-trial-data-idUSKCN25E1G7> (accessed on December 10, 2020)

<sup>38</sup> Vanda Pharmaceuticals, Form 8-K filing with the U.S. Securities and Exchange Commission, February 6, 2019, <https://vandapharmaceuticalsinc.gcs-web.com/node/8576/html> (accessed on December 11, 2020)

<sup>39</sup> Li Pang et al. (October 10, 2019), "Workshop Report: FDA Workshop on Improving Cardiotoxicity Assessment With Human-Relevant Platforms," Circ Res. 2019;125(9):855–67, doi: 10.1161/CIRCRESAHA.119.315378



Study title/ number **A 28-Day Toxicity Study** administered by Oral Capsule to Male Dogs with a 28-Day Recovery Period (study# VUM00005)

Key Study Findings • **Early euthanasia** mg/kg/day due to instances of convulsions;

**Convulsions (lasting up to 3 minutes), intermittent tremors**

- Pathologic changes consistent with findings in longer-term studies in dogs (epididymides, prostate, and testes).

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

#### Methods

Dose and frequency of dosing: 0, 5, 10, 25\* mg/kg/day, once daily for 28 days

\*The last dose administration at 25 mg/kg/day was conducted on Day 8, and the surviving animals were considered on recovery from Day 9 until termination on Day 29 or 57.

Route of administration: Oral, gelatin capsules

Formulation/Vehicle: (b) (4)

Species/Strain **Male beagle dogs**

Number/Sex/Group: 5/group (main), 3/group (recovery, control, MD, HD)

Age: not provided

Satellite groups/ unique design: none

Deviation from study protocol

affecting interpretation of results: No

#### **Observations and Results:**

Parameters	Major findings
Mortality	<b>animals were euthanized due to adverse clinical signs</b>
	Day 9 (#D3934).

Other experts raise this problem, too, writing: “Two critical ‘wrong’ decisions regarding animal tests of human pharmaceuticals are 1) falsely identifying a toxic drug as ‘safe’ and 2) falsely labeling a potentially useful therapeutic agent as toxic.”<sup>40</sup>

<sup>40</sup> Gail A. Van Norman (November 2019), “Limitations of Animal Studies for Predicting Toxicity in Clinical Trials: Is it Time to Rethink Our Current Approach?” JACC. Basic to translational science, 2019-11, Vol.4 (7), p.845-854, <https://doi.org/10.1016/j.jacbts.2019.10.008>

The diet drug fen-phen presents one famous, and famously tragic, example of how animal testing can cause false confidence in a drug's safety for humans.<sup>41</sup> Fen-phen appeared safe in animal models, and was approved for use by the FDA. Only after being widely prescribed to 6 million hopeful patients eager to shed pounds, was it discovered the so-called “‘miracle’ turned nightmare” drug caused life-threatening heart disease in many of those who took it.<sup>42</sup>



More recently, a drug called BIA 10-2474—being developed to treat Parkinson's disease, chronic pain, and other conditions—had its human trials halted in 2016 after one volunteer died, another was declared brain dead, and four more were hospitalized with serious brain damage.<sup>43</sup> The drug had been tested already on four animal species, including dogs (as well as rats, mice, and monkeys).<sup>44</sup>

A panel of medical experts studying this drug noted prior examples of “drugs with proven safety and efficacy in nonclinical animal models may exhibit different pharmacological properties when used in humans.” They propose this as an explanation in the case of BIA 10-2474 as well, “where the safety studies done in animal studies predicted it to be safe for human use but due to species variation some of the adverse effects could not be very well predicted.”<sup>45</sup>

That drugs would behave differently in humans and other animals, including dogs, is exactly what we should expect.

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<sup>41</sup> Science, Medicine, and Animals (2004), Washington, DC: The National Academies Press.

<https://doi.org/10.17226/10733>, <https://www.ncbi.nlm.nih.gov/books/NBK24645/> (accessed on December 10, 2020)

<sup>42</sup> John Fauber, “Slippery Slope: Fen-Phen Users Recall a ‘Miracle’ Turned Nightmare,” MedPage Today, April 19, 2015, <https://www.medpagetoday.com/special-reports/slipperslope/51044> (accessed on December 11, 2020)

<sup>43</sup> Martin Enserink, “French company bungled clinical trial that led to a death and illness, report says,” Science, February 6, 2016, <https://www.sciencemag.org/news/2016/02/french-company-bungled-clinical-trial-led-death-and-illness-report-says> (accessed on December 11, 2020)

<sup>44</sup> Gareth Macdonald, “Bial cannot rule out link between BIA 10-2474 and lung lesions in study dogs,” Outsourcing-pharma.com, February 26, 2016, <https://www.outsourcing-pharma.com/Article/2016/02/26/Bial-cannot-rule-out-link-between-BIA-10-2474-and-lung-lesions-in-study-dogs> (accessed on December 11, 2020)

<sup>45</sup> Rimplejeet Kaur, Preeti Sidhu, Surjit Singh (July-September 2016), “What failed BIA 10-2474 Phase I clinical trial? Global speculations and recommendations for future Phase I trials,” J Pharmacol Pharmacother. 2016 Jul-Sep; 7(3): 120–126. doi: 10.4103/0976-500X.189661

A pathologist forcefully made this point in a recent op-ed:<sup>46</sup> “If it’s clear how the thousands of dogs experimented on and killed to comply with this FDA red tape are harmed, what may be less obvious at first glance is how people are harmed, too—primarily by keeping safe and effective drugs from patients who need them, allowing dangerous drugs to reach the market and significantly increasing medical costs.”

Even the National Institutes of Health admits these problems, acknowledging that “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.”<sup>47</sup>

**The FDA’s dog testing mandate is unscientific.** “We have moved away from studying human disease in humans,” former NIH Director Dr. Elias Zerhouni said, in what has become a famous address to the agency on the limitations of animal models, five years after the end of his directorship:

“‘We all drank the Kool-Aid on that one, me included.’ With the ability to knock in or knock out any gene in a mouse—which ‘can’t sue us,’ Zerhouni quipped—researchers have over-relied on animal data. ‘The problem is that it hasn’t worked, and it’s time we stopped dancing around the problem...We need to refocus and adapt new methodologies for use in humans to understand disease biology in humans.’”<sup>48</sup>

Perhaps the most salient and common criticism of the FDA’s dog testing mandate is that it results in such grave harms to so many parties—for absolutely no valid purpose, and with no corresponding advantages, since the required animal tests do not aid in their intended goal of distinguishing drugs that are safe and effective from those that are not.

Criticized since the early 1960s, experts find the FDA’s animal testing requirements to be “ineffective, misleading to scientists, unable to prevent the development of dangerous drugs, and prone to prevent the development of useful drugs.”<sup>49</sup>

This is a view shared by government scientists. The government’s own findings show more than 95 percent of drugs that pass FDA-mandated animal tests fail in humans, because they are found to be ineffective or dangerous.<sup>50</sup>

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<sup>46</sup> Tiffani Milless, “FDA-required tests on puppies slow progress to COVID treatment,” AlterNet, September 08, 2020, <https://www.alternet.org/2020/09/fda-required-tests-on-puppies-slows-progress-to-treatment/> (accessed on December 11, 2020)

<sup>47</sup> National Institutes of Health, “NIH-Wide Strategic Plan Fiscal Years 2016-2020,” NIH website, December 16, 2015, <https://www.nih.gov/sites/default/files/about-nih/strategic-plan-fy2016-2020-508.pdf> (accessed on December 11, 2020)

<sup>48</sup> Rich McManus, “Ex-Director Zerhouni Surveys Value of NIH Research,” NIH Record, June 21, 2013, <https://nihrecord.nih.gov/sites/recordNIH/files/pdf/2013/NIH-Record-2013-06-21.pdf> (accessed on December 11, 2020)

<sup>49</sup> Kramer, Greek “Human Stakeholders and the Use of Animals in Drug Development,” 3

<sup>50</sup> National Institutes of Health, “Transforming Translational Science,” NIH website, 2019, [https://ncats.nih.gov/files/NCATS\\_Factsheet\\_508.pdf](https://ncats.nih.gov/files/NCATS_Factsheet_508.pdf) (accessed on December 23, 2020)

4-week – Dog (Study 0100044) Oral Toxicity x-1006A Following 28 Consecutive Administrations with a 14-Day Recovery Period and BioAnalysis Male and Female Beagle Dogs

Beagle dogs (N=3/sex/group Con, LD, MD; + 2/sex Con & HD 14-day recovery) were given 0, 10, 100, or 300 mg/kg/day Fx-1006A via oral gavage in 0.5% methylcellulose at 10 mL/kg once daily for 28 days.

Due to toxicity, HDF (Day 7) and HDM (Day 8) received no dose for one day, then resumed at a dose level of 200 mg/kg for the remainder of the study.

Vomiting and aspiration of the test article immediately postdose and subsequent death or moribund sacrifice occurred in 1/3 MDM (D20), 1/4 HDM (D7), and 1/4 HDF (D7). One additional MDM was found dead on D11 without showing any clinical signs or decreases in body weight or food consumption, and one additional HDM was found dead on D11 after showing mild vomiting effects and salivation (D9-10).

green discolored feces (0); thin, cold to touch, lethargic, vomiting, body weight loss (0-25%, scant food consumption (D12-D21); decreased lymphocytes; and increased AST, ALT, BUN, GGT and TBIL compared to baseline; the cause of death in these two animals was unknown. Soft/mucoid feces and vomiting were increased in LD, MD, and HD groups compared to Con. MD and HD animals showed increased incidence of salivation and lethargy.

Clinical signs in HD animals also included ataxia, head bobs, and twitching showed increased ALT, ALK, BUN, GGT and TBIL compared to Con. M while HD showed increased ALK compared to controls and baseline. Four of the HD animals showed red discoloration or thickening of some or all lobes of the tongue, associated with pulmonary congestion.

early death

**Effective and humane alternatives exist, and drug companies should be encouraged rather than prohibited from pursuing them.**

New technologies have demonstrated advantages over animal models. One 2019 study co-authored by researchers from major pharmaceutical companies used drugs that failed in humans and found that organs-on-chips—miniaturized organs built from human

<sup>53</sup> Van Norman, “Limitations of Animal Studies for Predicting Toxicity in Clinical Trials: Is it Time to Rethink Our Current Approach?”



cells that can be used to model diseases and test drugs—accurately predicted the human toxicities when animal tests didn't.<sup>54</sup>

Studies show that other high-tech alternatives like “microdosing,”<sup>55</sup> computer models,<sup>56</sup> and even “mini-brains”<sup>57,58</sup> present the opportunity for more efficient and more effective testing than the FDA’s required dog tests—if FDA bureaucrats would allow it.

Oxford University researchers wrote in *Scientific American* about their computer models that better predict adverse drug effects than tests on dogs and other animals.<sup>59</sup> They wrote, “human computational models would bring additional advantages by reducing the use of animal experiments in early stages of drug testing; improving drug safety, thereby lowering the risk for patients during clinical trials; and speeding up the development of medicines for patients in urgent need of healthcare.”

FDA scientists have adopted this position, as well: “The use of these new in vitro preclinical models has been accepted for investigational new drug applications and has great potential to reveal mechanisms of drug-drug interactions and personalize cardiac safety predictions. We think that current pharmaceutical cardiovascular safety assessment would benefit from an approach that may prove to be more efficient in cost and time, mechanistically informative, and translatable to human patients. Such an approach may enable the earlier recognition of development-limiting safety liabilities, reduction of false positives that lead to premature and unnecessary development termination, discovery of more relevant biomarkers, and a significant decrease of late-stage attrition.”<sup>60</sup>

So why is the FDA still requiring dog testing? Congress has demanded answers about exactly that but has yet to receive any answers.<sup>61</sup> In the meantime without that transparency or insight into the FDA’s NDA approval process, regulatory inertia seems the prime candidate.

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<sup>54</sup> Kyung-Jin Jang et al. (November 6, 2019), “Reproducing human and cross-species drug toxicities using a Liver-Chip,” *Science Translational Medicine*: Vol. 11, Issue 517, eaax5516 DOI: 10.1126/scitranslmed.aax5516 (accessed on December 23, 2020)

<sup>55</sup> Celia Henry Arnaud, “In The Search For New Drugs, Diverging Roads For Microdosing,” *Chemical & Engineering News*, January 21, 2013, <https://cen.acs.org/articles/91/i3/Search-New-Drugs-Diverging-Roads.html> (accessed on December 11, 2020)

<sup>56</sup> Richard Van Noorden, “Software beats animal tests at predicting toxicity of chemicals,” *Nature*, July 11, 2018, <https://www.nature.com/articles/d41586-018-05664-2> (accessed on December 11, 2020)

<sup>57</sup> Bret Stetkam “Lab-Grown “Mini Brains” Can Now Mimic the Neural Activity of a Preterm Infant,” *Scientific American*, August 29, 2019, <https://www.scientificamerican.com/article/lab-grown-mini-brains-can-now-mimic-the-neural-activity-of-a-preterm-infant/> (accessed on December 11, 2020)

<sup>58</sup> “‘Mini-brains’ Could Reshape Brain Research, Drug Testing,” Johns Hopkins University Department of Environmental Health and Engineering website, <https://ehe.jhu.edu/events-and-seminars/mini-brains-drug-testing.html> (accessed on December 11, 2020)

<sup>59</sup> Elisa Passini, Blanca Rodriguez, Patricia Benito, “Should Computer Simulations Replace Animal Testing for Heart Drugs?” *Scientific American*, March 27, 2018, <https://www.scientificamerican.com/article/should-computer-simulations-replace-animal-testing-for-heart-drugs/> (accessed on December 11, 2020)

<sup>60</sup> Pang et al., “Workshop Report: FDA Workshop on Improving Cardiotoxicity Assessment With Human-Relevant Platforms”

<sup>61</sup> Carlin Becker, “Bipartisan group of lawmakers demands answers on FDA requiring companies to test on dogs,” *Washington Examiner*, July 22, 2020, <https://www.washingtonexaminer.com/news/bipartisan-group-of-lawmakers-demands-answers-on-fda-requiring-companies-to-test-on-dogs> (accessed on December 11, 2020)

“Bureaucracy plays a large part in the delay to the implementation of alternatives, in my view, particularly at the regulatory acceptance stage,” observes one expert in a recent paper:

“It is, in my opinion, in part caused by inertia amongst regulators and a failure to incentivize and reward them for evaluating new methods. The process still largely relies on the goodwill of a few experts from a few countries. Industry are not specifically rewarded for developing alternatives and, indeed, run some risk if the alternative is not accepted (due to wasted development costs).”<sup>62</sup>

The FDA should and can overcome the institutional roadblocks or other hurdles standing in the way of progress, to encourage the development and use of these alternative methods, in order to bring drug testing into the 21<sup>st</sup> century rather than hewing to the expensive, outdated, unscientific, pointless, cruel, and harmful animal testing model.

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<sup>62</sup> Katy Taylor, “Recent Developments in Alternatives to Animal Testing,” in *Animal Experimentation: Working Towards a Paradigm Change* (Brill, 2019), pp.585-609

## FDA's Current Reform Efforts

Following calls from WCW, taxpayers, scientists, industry, and Congress to cut FDA dog testing red tape, then-FDA Commissioner Dr. Stephen Hahn wrote on Twitter:

"FDA is committed to fostering innovation. As part of this commitment, we are working to develop new regulatory tools that can help improve predictivity and potentially replace, reduce and/or refine animal testing in medical product development."<sup>63</sup>



Similarly, the FDA's official account tweeted that cutting-edge technologies "may help replace, reduce and refine animal testing, helping to bring FDA-regulated products to market faster, with improved efficacy, or prevent products with increased toxicological risk from reaching the market."<sup>64</sup>

While additional reforms are urgently needed and long overdue, the FDA has made some encouraging movement toward cutting FDA red tape and allowing companies to use alternatives to dog testing.<sup>65</sup> These include:

- Reassessing the use of dogs in testing for food additive safety, and finding the use of dogs to be unnecessary.<sup>66</sup>
- Working to reduce the terminal use of dogs in testing veterinary drugs.<sup>67</sup>
- Allowing several COVID-19 drugs to advance to human clinical trials without waiting for animal tests.<sup>68</sup>

<sup>63</sup> Stephen Hahn, Twitter post, January 5, 2021, <https://twitter.com/SteveFDA/status/1346557845957914627> (accessed on January 7, 2021)

<sup>64</sup> Food and Drug Administration, Twitter post, August 14, 2020, [https://twitter.com/US\\_FDA/status/1294316534022770688](https://twitter.com/US_FDA/status/1294316534022770688) (accessed on December 11, 2020)

<sup>65</sup> Food and Drug Administration, "FDA Publishes Report on Advancing Alternative Methods," FDA website, January 5, 2021, <https://www.fda.gov/news-events/fda-brief/fda-brief-fda-publishes-report-advancing-alternative-methods>

<sup>66</sup> Suzanne C. Fitzpatrick, "Update on CFSAN Toxicology Activities," FDA website, December 3, 2019, <https://www.fda.gov/media/132933/download> (accessed on December 11, 2020)

<sup>67</sup> Food and Drug Administration, "FDA Proposes Study with Intent of Eliminating Use of Dogs in Certain Types of Research," FDA website, November 16, 2018, <https://www.fda.gov/animal-veterinary/cvm-updates/fda-proposes-study-intent-eliminating-use-dogs-certain-types-research> (accessed on December 11, 2020)

<sup>68</sup> Eric Boodman, "Researchers rush to test coronavirus vaccine in people without knowing how well it works in animals," STAT, March 11, 2020, <https://www.statnews.com/2020/03/11/researchers-rush-to-start-moderna-coronavirus-vaccine-trial-without-usual-animal-testing/> (accessed on December 11, 2020)

- Creating an Alternatives Methods Working Group focused on developing opportunities for new technologies to be used in place of animal testing to fulfill regulatory requirements.<sup>69</sup>
- Launching a new alternatives webinar series for those developing new technologies to share their methods and practices with FDA scientists and regulators.<sup>70</sup>
- Investing in the development of high-tech alternatives to animal testing, like organs-on-chips technology.<sup>71</sup>

Unfortunately, these ongoing initiatives, while important, lack concrete timelines and performance indicators to measure progress and success. A 2019 Government Accountability Office audit of federal animal testing programs—prompted by a WCW investigation and pressure from Congress—documented this failure as well.<sup>72</sup> Without more transparency and accountability, there remains a lack of clarity for Congress, taxpayers, and industry about how and when the FDA will actually begin widespread

adoption and regulatory acceptance of these new technologies to replace animal testing that companies are increasingly relying on to screen drugs.

**6.2.2 Non-rodent**  
**Exploratory Studies in Dogs**  
**Study title: NBI-98854 and NBI-98782: A 14-Day Oral (Capsule) Toxicity Study in Dogs Dogs with a Minimum of 1-Week Recovery Period**  
 Study no.: 08-3332  
 Study report location: SDN 1 (eCTD 0000), 4/29/2016  
 Conducting laboratory and location: (b) (4)  
 Date of study initiation: 5/20/2008  
 GLP compliance: Yes  
 QA statement: Yes  
 Drug, lot #, and % purity: Valbenazine, 08KL014D, 98.7%

**Key Study Findings**  
 Valbenazine treatment-related **mortality** red at the 35 mg/kg/day dose level. The top dose was lowered to 30 mg/kg/day on day 11.  
 Adverse valbenazine treatment-related toxicity consisted of the following:

- Clinical signs at 35/30 mg/kg/day: **seizure-like activity (jerky/uncoordinated movement, convulsions), trembling, ataxia, difficulty standing, head bobbing, weak pulse, and excessive salivation**
- The Sponsor judged the NOAEL to be 15 mg/kg/day due to mortality and clinical signs observed at the highest dose, corresponding to a C<sub>max</sub> of 6470 and 9410 ng/mL and an AUC<sub>0-24</sub> of 31900 and 36400 ng•hr/mL in males and females, respectively.
- This reviewer judged the NOAEL to be 5 mg/kg/day, based on clinical signs **CNS depression, muscle tremors** ted at 15 mg/kg/day.

Indeed, the COVID-19 pandemic has demonstrated that the FDA has the authority and ability to allow companies to bypass unnecessary animal testing, and that doing so will expedite drug development and approval. In the case of several safe and effective COVID-19 vaccines now on the market, the FDA allowed the drugs to be tested on humans

without first completing testing on animals.

<sup>69</sup> Food and Drug Administration, "FDA Webinar Series on Alternative Methods: Showcasing cutting-edge technologies for disease modeling, efficacy, and safety," FDA website, May 20, 2020, <https://www.fda.gov/science-research/about-science-research-fda/fda-webinar-series-alternative-methods-showcasing-cutting-edge-technologies-disease-modeling> (accessed on December 11, 2020)

<sup>70</sup> Food and Drug Administration, "FDA Webinar Series on Alternative Methods: Showcasing cutting-edge technologies for disease modeling, efficacy, and safety," FDA website, May 20, 2020, <https://www.fda.gov/science-research/about-science-research-fda/fda-webinar-series-alternative-methods-showcasing-cutting-edge-technologies-disease-modeling> (accessed on December 23, 2020)

<sup>71</sup> Bob Woods, "It sounds futuristic, but it's not sci-fi: Human organs-on-a-chip," CNBC, August 15, 2017, <https://www.cnbc.com/2017/08/14/fda-tests-groundbreaking-human-organs-on-a-chip.html> (accessed on December 24, 2020)

<sup>72</sup> Government Accountability Office, "ANIMAL USE IN RESEARCH: Federal Agencies Should Assess and Report on Their Efforts to Develop and Promote Alternatives," GAO website, September 24, 2019, <https://www.gao.gov/products/GAO-19-629> (accessed on February 9, 2021)



Back in March 2020, in the early days of the pandemic, Moderna Therapeutics' chief medical officer Dr. Tal Zaks stated, "I don't think proving this in an animal model is on the critical path to getting this to a clinical trial."<sup>73</sup>

It now appears Zaks was right. In December 2020, the FDA approved Moderna Therapeutics' COVID-19 vaccine after it showed 94.5 percent effectiveness at preventing infection in human trials.<sup>74</sup>

As of the end of March 2021, Moderna says it has already shipped some 116 million doses of its vaccine to the United States. Another 100 million doses are expected by the end of May, with millions more coming in the months after that.<sup>75</sup>

This desperately needed vaccine could not have been developed and brought to market so quickly had the FDA forced Moderna to waste time and other resources testing on animals before the drug could enter human trials. Some animal testing was concurrently conducted with the human trials, but was wasteful and unnecessary given the drug was already being safely administered to humans based on non-animal research.

COVID response leader Anthony Fauci, NIH Director Francis Collins, and then-U.S. Secretary of Health and Human Services Alex Azar all received the Moderna vaccine, demonstrating their faith in the process that sidelined animal tests.<sup>76</sup>

This regulatory flexibility appears to be paying off in the face of an urgent public health and economic crisis. These are encouraging first steps, as one economist wrote in the Financial Times:<sup>77</sup>

"Insisting on unreliable animal tests means patients, taxpayers, investors and many others will continue to suffer harm while potentially safe and effective drugs, even for Covid-19, collect dust on the shelf. It's time to deregulate and give pharmaceutical companies the freedom to employ the best tools science has to offer."

There is, indeed, no reason for the FDA not to do so. Drug companies should not be prohibited from testing on dogs if they determine it's necessary, but applying good science and policy, testing on dogs should not be required.

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<sup>73</sup> Boodman, "Researchers rush to test coronavirus vaccine in people without knowing how well it works in animals"

<sup>74</sup> Denise Grady, Abby Goodnough, Noah Weiland, "F.D.A. Authorizes Moderna Vaccine, Adding Millions of Doses to U.S. Supply," New York Times, December 18, 2020, <https://www.nytimes.com/2020/12/18/health/covid-vaccine-fda-moderna.html> (accessed on December 24, 2020)

<sup>75</sup> "Moderna Says Shipped 100 Million COVID-19 Vaccine Doses to United States," Reuters, March 29, 2021, <https://www.usnews.com/news/top-news/articles/2021-03-29/moderna-says-shipped-100-million-covid-19-vaccine-doses-to-united-states> (accessed on April 2, 2021)

<sup>76</sup> Andrea Diaz, "Fauci, Collins and Azar receive their first doses of Covid-19 vaccine," CNN, December 22, 2020, <https://www.cnn.com/2020/12/22/health/fauci-azar-collins-vaccinated-covid-19/index.html> (accessed on January 7, 2021)

<sup>77</sup> Lisa Kramer, "Testing drugs for humans on dogs makes no sense," Financial Times, July 17, 2020, <https://www.ft.com/content/4c19e68b-4b38-405b-b052-852d41cec49a>

## Bipartisan Congressional Support for Reform

In July 2020, 18 members of Congress, led by Reps. Brendan Boyle (D-PA) and Scott Perry (R-PA), fired off a bipartisan letter to Dr. Stephen M. Hahn, then-Commissioner of the FDA, demanding answers about why agency bureaucrats are forcing drug makers to navigate red tape when cutting it would “save time, money and dogs, and accelerate medical innovation.”<sup>78</sup>



This was followed by action in the Senate, where Sens. Susan Collins (R-ME), a member of the FDA’s Senate funding panel, and Martha McSally (R-AZ) dispatched a letter to then-FDA Commissioner Hahn calling for the FDA to “prioritize finding alternatives to drug testing on dogs.”<sup>79</sup>

These letters have been accompanied by significant bipartisan legislative action, starting with the FDA’s 2021 spending bill. The bill signed into law included a measure directing the agency to issue a report describing how drug makers can avoid the dog

<sup>78</sup> Reps. Brendan F. Boyle (D-PA), Scott Perry (R-PA), et al. to FDA Commissioner Dr. Stephen Hahn, July 22, 2020, <https://blog.whitecoatwaste.org/wp-content/uploads/2020/07/Letter-to-FDA-re-dog-testing-requirements-7.22.20.pdf> (accessed on December 23, 2020)

<sup>79</sup> Carlin Becker, “FDA Under Pressure to Cut Dog-Testing Requirement in Search for Covid Cure”

testing mandate in favor of more efficient and effective alternatives, and to revise its outdated and burdensome regulations.<sup>80</sup>

In November 2020, Reps. Boyle, Perry, and Madeleine Dean (D-PA) also introduced the Alternatives to Animals for Regulatory Fairness Act (H.R.8736 in the 116<sup>th</sup> Congress). This bill, known as the AARF Act, would give drug companies the freedom to avoid the FDA's dog testing mandate.<sup>81</sup> The bill was reintroduced in the 117<sup>th</sup> Congress (H.R. 1905) by Reps. Boyle, Dean and Brian Fitzpatrick (R-PA).<sup>82</sup>

Specifically, the AARF Act would amend the woefully outdated Food, Drug, and Cosmetic Act to reflect that alternatives to dog and other animal tests can be used if they fulfill relevant requirements—which is what FDA guidance states, but the guidance does not carry the force of law and is often ignored by regulators.

“Current government policies that force pharmaceutical companies to waste time and money on outdated animal testing must immediately be eliminated,” said Rep. Perry, on the bill's introduction. “I'm proud to lead this effort to leverage modern technology and improve our drug approval process to benefit patients, protect animals, and accelerate medical innovation. I thank Reps. Boyle and Dean for their partnership on this common-sense solution to bring cures and treatments to market while also protecting dogs and other animals.”<sup>83</sup>

These bipartisan lawmakers have made cutting FDA red tape part of their public agenda, frequently posting about this campaign on Facebook and other social media—reflecting their commitment to the issue, and their constituents' growing engagement.<sup>84</sup>

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<sup>80</sup> Arin Greenwood, “#CUTFDAREDTAPE PROGRESS! CONGRESS DEMANDS FDA REPORT ON AVOIDING WASTEFUL DOG TESTING, UPDATES TO OUTDATED REGULATIONS,” White Coat Waste Project website, July 8, 2020, <https://blog.whitecoatwaste.org/2020/07/08/cutfdaredtape-progress-congress-demands-fda-report-on-avoiding-wasteful-dog-testing/> (accessed on December 11, 2020)

<sup>81</sup> Eliza Erskine, “New Bill Introduced to End FDA Dog Testing,” One Green Planet, November 16, 2020, <https://www.onegreenplanet.org/animalsandnature/new-bill-introduced-to-end-fda-dog-testing/> (accessed on December 11, 2020)

<sup>82</sup> “Reps. Boyle, Dean and Fitzpatrick Introduce Bipartisan Animal Testing Alternatives Legislation,” March 16, 2021, press release on Congressman Brendan Boyle's website, <https://boyle.house.gov/media-center/press-releases/boyle-dean-fitzpatrick-introduce-bipartisan-animal-testing> (accessed on April 2, 2021)

<sup>83</sup> “Perry, Boyle, and Dean Introduce Bipartisan Animal Testing Alternatives Legislation,” November 20, 2020, press release on Congressman Scott Perry's website, <https://perry.house.gov/news/documentsingle.aspx?DocumentID=402510> (accessed on December 11, 2020)

<sup>84</sup> See, for example, Rep. Brendan Boyle's Tweet posted on August 26, 2020, <https://twitter.com/CongBoyle/status/1298719307468140544>, and Rep. Scott Perry's Facebook post from August 26, 2020, <https://www.facebook.com/repsscottperry/posts/3393601890736075> (both accessed on December 24, 2020)

## WCW Conclusion and Recommendations

“By not changing its outmoded approach of forcing companies to conduct unnecessary tests on dogs, the FDA not only misses the opportunity to improve safety, but also pointlessly impedes the delivery of innovative new drugs to patients who need them,” says Vanda Pharmaceuticals CEO Dr. Mihael Polymeropolous.<sup>85</sup>

The puppies are just one week old when experimental drugs are forced through a tube into their stomachs, or injected into their eyes. These trusting animals will endure this abuse for up to a year, before they are killed.

Drug companies’ own scientists would rather use the newer, cheaper, faster, more accurate, and more humane alternatives—except the FDA, by and large, remains entrenched in practices from nearly a century ago.

White Coat Waste Project finds the FDA’s red tape must be cut to modernize regulations better suited for today’s public health and business needs.

**WCW offers the following recommendations to cut FDA red tape and spare dogs, stop waste, spur innovation, and save lives:**

- **Audit the FDA:** The Government Accountability Office should audit the FDA to determine the extent to which the FDA has—or has not—allowed companies to use alternatives to dog tests, what metrics the agency uses to assess the effectiveness of its programs to curb mandated testing on dogs, and what improvements can be made to reduce wasteful dog tests.
- **Enact the AARF ACT:** Congress should pass the bipartisan Alternatives to Animals for Regulatory Fairness Act (H.R. 1905 in the 117<sup>th</sup> Congress)—known as the AARF Act—to codify drug companies’ freedom to avoid the FDA’s dog testing mandate and utilize more productive testing methods.
- **Modernize regulations and industry guidances:** The FDA should revise its current regulations and issue detailed guidance on how drug makers can avoid testing on dogs under the current legal framework.
- **Enhance accountability:** The FDA’s Alternative Methods Working Group should establish performance indicators and timelines for its efforts to expand regulatory acceptance of non-dog testing methods.

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<sup>85</sup> Carlin Becker, “FDA Under Pressure to Cut Dog-Testing Requirement in Search for Covid Cure,” Zenger, November 11, 2020, <https://www.zenger.news/2020/11/11/fda-under-pressure-to-cut-dog-testing-requirement-in-search-for-covid-cure/> (accessed on December 11, 2020)