

January 31, 2008

Andrew C. von Eschenbach, M.D.
Commissioner
U.S. Food and Drug Administration
U.S. Department of Health and Human Services
5600 Fishers La., Rm. 15-47
Rockville, MD 20857

3 pages via mail and fax: 301-443-3100

Dear Dr. von Eschenbach,

Recent scientific opinion, such as that expressed by the National Research Council in its recent report titled “Toxicity Testing in the Twenty-First Century: A Vision and a Strategy,”¹ recognizes deep flaws in the drug-approval process stemming primarily from the inability of animal-based toxicity testing to predict the real danger of new substances to humans. In a 2004 White Paper titled “Innovation or Stagnation? Challenge and Opportunity on the Critical Path to New Medical Products,”² the Food and Drug Administration (FDA) acknowledged that 92 percent of compounds that pass animal tests go on to fail in human clinical trials. The FDA’s Critical Path Initiative is intended to address these flaws by modernizing the scientific tools that are involved in bringing new drugs to market. These issues are also of tremendous importance to PETA’s more than 1.8 million members and supporters, who care about the animals who suffer in laboratory experiments. We are concerned about how the archaic toxicity testing paradigm—combined with a sloppy and inconsistent regulatory system—impacts the lives of millions of animals every year.

The FDA’s current lack of transparent drug-approval standards and its failure to recognize the many superior non-animal testing methods lead the pharmaceutical industry to hedge its bets. Companies perform excessive animal tests beyond what the FDA might recommend to ensure that their new-drug investment is protected and to ensure that they get the positive results from the testing that they want. If they conduct enough tests and those tests are inconsistent enough, they will eventually get a successful outcome—and there is no requirement to report the failures. The FDA facilitates this excessive use of animals by failing to penalize the behavior. In fact, it encourages companies to go “above and beyond” the prescribed animal-testing regimen, despite the fact that the FDA has a legal and ethical obligation under the Animal Welfare Act (AWA) and the implementation guidelines to the 1993 NIH Revitalization Act³ to reduce the number of animals used and to carefully consider each and every use of animals.

A few specific examples that illustrate the failures of the current system to consider animal welfare include the following:

1. Continued Acceptance of Single-Dose Acute Toxicity Testing

A working group of 18 European pharmaceutical companies recently conducted an evidence-based review of the relevance of acute toxicity studies in the drug discovery process and concluded that the studies do not provide pivotal information for human safety assessment and should be discontinued.⁴ This review has already led to a 70 percent reduction in animal use in acute toxicity testing by the companies that were involved in the study, and the recommendations of the working group are currently being incorporated into International Conference on Harmonisation (ICH) guidance documents.⁵ While the FDA has stated that it supports the use of *in vitro* cytotoxicity tests to reduce the number of animals who are killed in lethal dose testing, it has also clearly stated that the agency does not specifically solicit lethality data.⁶ In a 2006 workshop covering the recent European review, the FDA also expressed support for the discontinuation of acute toxicity studies.⁷ However, the FDA has yet to incorporate these



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sentiments into its guidance for industry nor has it made any efforts to discourage companies from using acute toxicity data as a mainstay of their application packages.

2. Continued Acceptance of Dose Response Data vs. STD10 (Severe Toxic Dose 10%)

Although the FDA does not require a complete toxic dose determination in dogs if it is demonstrated that one-tenth of the STD10 is tolerated in rodents, most companies still conduct the complete study in dogs because contract toxicology labs promote these tests. The FDA could easily rectify this situation by notifying companies that it will no longer condone the extra testing.

3. Lack of Verification That the Second Species Is Necessary

The FDA still recommends that many of the toxicity tests of new drugs be done in two species, despite the fact that only one species provides the information that is required for a new drug application. The decision to require dual-species testing is completely arbitrary in many cases and only serves to greatly increase the number of animals that are used.

4. Inconsistency in the Length of Chronic Studies in Dogs

The length of chronic toxicity studies in dogs has been scrutinized by many regulatory agencies, including the ICH. Although the FDA has adopted the ICH's determination that nine months is a sufficient maximum time to assess chronic toxicity for almost all new drugs,⁸ many companies continue to make dogs suffer for many more months to years. The FDA has failed to communicate that it considers dog studies that are longer than nine months to be superfluous.

5. Rampant Use of Dogs

The use of dogs in toxicity testing is especially objectionable to most Americans because of the integral relationship that we have with these animals. Unfortunately, a huge industry has been built around the breeding, poisoning, and killing of dogs for toxicity testing, and that industry has a clear vested interest in promoting as many tests on dogs as possible. The fact that the FDA accepts the excessive testing promoted by the breeders and contract testing labs illustrates a tragic lack of leadership and respect for the AWA.

6. Withholding of an Updated Medical Devices Compendium

In 1997, the FDA's Center for Devices and Radiological Health (CDRH) compiled an unofficial list of medical-device components that were known to be safe in humans. However, because this list was not codified and has not been updated, individual manufacturers continue to test each component of a new device on animals *de novo*. PETA has urged the FDA to update and distribute a complete list of medical device materials that the CDRH established as being safe so that manufacturers no longer have to perform these redundant tests (letter sent to the CDRH director, November 9, 2007).

7. Continued Use of Inhumane Approaches to Rabies Vaccine Batch Testing

Despite the fact that a far superior non-animal test exists, every batch of rabies vaccine is currently tested for potency by a horribly cruel and unreliable test that uses mice. The only reason that the non-animal test has not been adopted is because the current validation method for any alternative requires that the test demonstrate the same reliability as the test that it is replacing. In this case, the non-animal alternative is so much more reliable that it can't replicate the unreliability of the mouse test (up to 400 percent variability is considered acceptable). PETA has suggested a different validation strategy to the FDA that would serve to circumvent this ridiculous situation, as well as to improve the safety of the rabies vaccine (letter sent to the Center for Biologics Evaluation and Research, Regulatory Coordinator, July 13, 2006).

8. Lack of Guidance in Shellfish Toxin Testing

Shellfish intended for use as food are routinely monitored for potentially deadly levels of toxins using animal tests. Although the FDA recognizes several non-animal tests for shellfish toxins, these tests have

not been incorporated into the FDA's guidance documents. Therefore, the shellfish industry often continues to use the decades-old test that uses mice. PETA has asked the FDA to codify its shellfish-testing policies so that these senseless animal tests will no longer be conducted simply because of the FDA's lack of guidance. Clarifying its policy would also bring the FDA in line with international regulatory agencies (letter sent to the Center for Food Safety and Applied Nutrition, Office of Science Director, December 9, 2005).

These examples, while not all-inclusive, are meant to illustrate the need for more thoughtful consideration of animal welfare issues and the need for the FDA to modernize its decision-making processes. A Citizens' Suit Petition, which was recently submitted to the FDA for Mandatory Use of Non-Animal Methods in the Development and Approval of Drugs and Devices (November 14, 2007), requests that the FDA modernize its policies (to match those in the European Union) by promoting the use of non-animal alternatives. We urge you to grant this petition and implement it with all due speed. The current reliance on animal experimentation shows a lack of innovation and common sense at the FDA. This failure not only results in the needless suffering and death of millions of animals but also endangers the health and lives of the millions of humans, as animal tests cannot adequately predict the effects of new substances in humans.

I look forward to hearing from you on this important matter. I can be contacted at 607-330-0564 or NancyD@peta.org.

Sincerely,



Nancy Douglas, Ph.D.
Regulatory Testing Division

¹National Research Council, "Toxicity Testing in the Twenty-First Century: A Vision and a Strategy," report of the Committee on Toxicity and Assessment of Environmental Agents, Jun. 2007.

²Food and Drug Administration, "Innovation or Stagnation? Challenge and Opportunity on the Critical Path to New Medical Products," White Paper, Mar. 2004.

³Public Law 103-43, NIH Revitalization Act of 1993, "Plan for Use of Animals in Research," 10 Jun. 1993.

⁴Sally Robinson, Kathryn Chapman, Jean-Luc Delongueas, Elizabeth Donald, David Dreher, Matthias Festag, Sophie Kervyn, Ann Lampo, Kamil Nahas, Vicente Nogueas, Deborah Ockert, Kirsty Quinn, Sally Old, Nigel Pickersgill, Kev Somers, Claudia Stark, Peter Stei, Lynne Waterson, "A European Pharmaceutical Company Initiative Challenging the Regulatory Requirement for Acute Toxicity Studies in Pharmaceutical Drug Development," *Regulatory Toxicology and Pharmacology*, available online 5 Dec. 2007.

⁵National Centre for the Replacement, Refinement, and Reduction of Animals in Research Acute Toxicity Workshop, "Challenging the Regulatory Requirement for Acute Toxicity Studies in the Development of New Medicines," report, London, Nov. 2006.

⁶Mark McClellan, FDA commissioner, letter to Kenneth Olden, National Institute of Environmental Health Science director, 9 Sept. 2003.

⁷National Centre for the Replacement, Refinement, and Reduction of Animals in Research Acute Toxicity Workshop, "Challenging the Regulatory Requirement for Acute Toxicity Studies in the Development of New Medicines," report, Appendix 2, London, Nov. 2006.

⁸Federal Register, "International Conference on Harmonisation; Guidance on the Duration of Chronic Toxicity Testing in Animals (Rodent and Nonrodent Toxicity Testing)," Docket No. 97D-0444, Vol. 64, No. 122, Jun. 1999.

June 19, 2008

Robin Levis, Ph.D.
Regulatory Coordinator
Center for Biologics Evaluation and Research (CBER)
Food and Drug Administration (FDA)
8800 Rockville Pike
Bethesda, MD 20892

Via electronic mail to: Robin.Lewis@fda.hhs.gov

Dear Dr. Levis,

I am a molecular biologist writing on behalf of the more than 2 million members and supporters of People for the Ethical Treatment of Animals. PETA and the scientists at the Institute for InVitro Sciences (IIVS) have worked together to identify an attainable validation study that will replace the use of animals for batch testing rabies vaccines. As you are aware, the mouse NIH test that is currently used for batch testing rabies vaccines uses 160 mice per batch, is extremely painful for the animals, and does not ensure human health protection due to the lack of reproducibility of the assay.

The currently required rabies potency test performed by CBER's labs involves a challenge procedure in which vaccinated and unvaccinated mice are injected with the live rabies virus directly into their brains. This test has scientific and ethical problems including a 400% variability of results, a non-biological route of infection, high expense, and acute pain and suffering for the mice. Not only does intracerebral injection cause extreme pain, but the test protocol causes 50% of the mice to develop rabies and then to die a slow and painful death characterized by neurological impairment, loss of motor control, paralysis of the limbs, convulsions, and significant weight loss from being unable to eat or drink.

Modern, analytical methods exist and have been used for many years in parallel to the NIH test. The most promising of these methods appears to be the ELISA (Enzyme-Linked Immunosorbant Assay) method which, as I understand, is frequently used by CBER but has not been formally validated and hence is not accepted as an official replacement method. Yet the ELISA test is able to quantify the amount of rabies coat glycoprotein in each vaccine batch and therefore is a much more precise and scientific method to assay rabies batch potency.

IIVS has attempted to contact you over the past few months to set up a meeting to discuss this potential collaboration to officially validate the ELISA test. I will follow up with you by phone in several days so that we can plan the timing of our meeting.

In the meantime, please do not hesitate to contact me about this important matter. I can be reached at 607.272.3143 or via email at SamanthaD@peta.org.

Sincerely,



Samantha Dozier, Ph.D.
Policy Advisor, Medical Testing Issues
Regulatory Testing Division



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July 15, 2008

Andrew C. von Eschenbach, M.D.
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Dear Dr. von Eschenbach,

People for the Ethical Treatment of Animals represents more than 2 million members and supporters who are concerned about suffering of animals in laboratory experiments and, in particular, the FDA's position on the use of animals for acute toxicity testing. Acute toxicity testing in animals is unpredictable and essentially useless for determining an acutely toxic dose for humans. In light of a recent meta-analysis, reviews, and a general movement away from using animals for acute toxicity testing in Europe, we would like to receive (1) a written statement regarding FDA's current position and guidance on acute toxicity testing; and (2) FDA's timeline to issue an updated, official position that precludes the use of animal testing for ascertaining acute toxicity.

The results from a collaborative meta-analysis published in a recent issue of *Regulatory Toxicology and Pharmacology* (Delongea, *et al.*, 2008) conclude that ample toxicity information "can be obtained from other studies, which are performed at more relevant doses for humans and are already an integral part of drug development."ⁱ

Accordingly, the latest draft of International Conference on Harmonisation (ICH) Guidance on Acute Toxicity Testing now includes the following recommendations:

- Acute toxicity studies in animals prior to the first clinical trials in humans are no longer required. In the majority of cases, stand-alone acute toxicity data should not be required.
- Lethality should not be the endpoint in these studies.
- Where acute toxicity data has been deemed necessary, the ICH draft now recommends that any short-term or dose-escalation data submitted be used to define a maximum tolerated dose rather than requiring *de novo* acute toxicity experiments.

For more than a quarter-century, notable experts have exposed the uselessness of acute toxicity tests:

“For the recognition of symptomatology of acute poisoning in man, and for the determination of the human lethal dose, the LD50 in animals is of very little value” (Zbinden and Flury Roversi, 1981)ⁱⁱ.

“ The test has never been formally validated. The widespread use of the test has therefore not been based on a documented good performance, but on lack of better tests” (Ekwall, *et al.*, 1998)ⁱⁱⁱ.



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“...even if the LD50 could be measured exactly and reproducibly, the knowledge of its precise numerical value would barely be of practical importance, because of extrapolation from the experimental animal is hardly possible” (Lorke, 1983)^{iv}.

Even when acute toxicity tests are performed on two relatively closely related rodents (rats and mice), results vary tremendously. Rats and mice shared a common ancestor 8-14 million years ago; however, the degree of data agreement is minimal at best. Humans and rodents shared a common ancestor 65 million years ago, making it even less likely that useful information can be gleaned from acute toxicity tests on animals. Results from tests on mice and rats are as follows (data analysis from the Physicians Committee for Responsible Medicine):

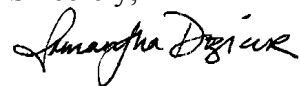
Chemical	Rat LD 50	Mouse LD50	Ratio (rat:mouse)
Carbon Tetrachloride	2,350	8,260	0.28
Dextropropoxyphene HCl	84	225	0.37
Dichloromethane	1,600	873	1.8
Diphenylhydantion	1,640	150	10.9
Ethanol	7,060	3,450	2.0
Mercury (II) Chloride	1	6	0.17
Nicotine	50	3	16.7
Paracetamol	2,400	340	7.0
Sodium Oxalate	11,200	5,100	2.2
Thioridazine HCl	995	385	2.6

To date, the FDA has shown a concerning lack of leadership in this arena and has not taken significant steps to reduce animal tests – even those tests that have been deemed useless by internationally recognized experts or otherwise shown to be scientifically unacceptable. For more information regarding PETA’s efforts to assist FDA in replacing unpredictable experimentation on mice, please see the attached letter regarding rabies vaccine efficacy testing.

We urge FDA to move away from animal-based experiments and hope to see FDA specify that acute toxicity studies in animals are no longer accepted.

We would appreciate a timely response to our specific questions regarding acute toxicity testing requirements at FDA. Please do not hesitate to contact me if you have any questions. I can be reached at 757-622-7382 ext. 8119 or via email at SamanthaD@peta.org

Sincerely,



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Policy Advisor, Medical Testing Issues
Regulatory Testing Division

ⁱ Delongeaas, et al. (2008). A European pharmaceutical company initiative challenging the regulatory requirement for acute toxicity studies in pharmaceutical drug development. *Regul Toxicol Pharmacol.* Apr; 50(3):345-52

ⁱⁱ Zbinden and Flury-Roversi (1981) Significance of the LD50 Test for the Toxicological Evaluation of Chemical Substances. *Archives Toxicol.* 47:77-99.

ⁱⁱⁱ B. Ekwall et al. (1998) MEIC evaluation of acute systemic toxicity. Part VI. The prediction of human toxicity by rodent LD50 values and results from 61 in vitro methods. *ATLA* 26:617-658

^{iv} D Lorke (1983). A new approach to practical acute toxicity testing. *Arch. Toxicol.* 54:275-287