Petition to the US Food and Drug Administration for Mandatory Use of Non-Animal Methods in the Development and Approval of Drugs and Devices

(Short Name: Mandatory Alternatives Petition)

EXECUTIVE SUMMARY
September 2007

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I. Purpose, Rationale and Scope

This petition seeks changes in US Food and Drug Administration (FDA) regulations and policies that would require, and not merely permit or recommend, that pharmaceutical companies, device manufacturers, and other entities regulated by the FDA submit data only from scientifically satisfactory non-animal test methods, and in lieu of corresponding animal test methods, whenever such scientifically satisfactory methods are available. Although there are sound scientific, economic and humane reasons why the use of scientifically satisfactory non-animal test methods should be mandatory, there is currently little incentive or support for researchers, businesses, regulatory agencies and educators to adopt them, or to develop new ones.

In contrast to the US, Europe has progressed in this area following European Union (EU) Directive 86/609/EEC in 1986. In particular, Article 7.2 states, "An experiment shall not be performed [on an animal], if another scientifically satisfactory method of obtaining the result sought, not entailing the use of an animal, is reasonably and practicably available." This requirement is legally binding on all EU member states. Adoption of a similar requirement in the US would go far toward harmonizing policy and practice on both sides of the Atlantic, as well as toward replacing animal use with scientifically satisfactory non-animal alternatives.

As set forth in this petition, the FDA has the authority to mandate the use of non-animal alternatives and to restrict the use of animal test methods for purposes of FDA approval. This petition requests that the FDA exercise this authority to promulgate a regulation mandating that investigators and testing facilities use scientifically satisfactory non-animal replacements for animal-based methods when meeting the requirements of the Federal Food, Drug and Cosmetic Act.

II. Current Practice: Advantages, Validation and Regulatory Approval of Alternative Methods

Non-animal test methods spare significant numbers of animals from pain and distress, are typically less costly and time-consuming, and may require lower investment in personnel and other resources. Most importantly, they often have more predictive value and specificity for the human condition. Examples of the superior predictive value of non-animal tests include the embryonic stem-cell test for embryotoxicity, new assays for skin corrosivity, in vitro tests for cancer causation and drug efficacy/toxicity at the US National Cancer Institute (NCI), and microdosing technologies. In fact, some 30 empirical studies have so far been published showing equal or greater efficacy for non-animal methods.

Animal test methods, many of which have been in use for decades, have never been scientifically validated. Despite this, a bias persists towards them, and with no true gold standard available they have typically been used as the default standard against which

non-animal tests are judged. In vitro data (as an example) may show only 55-80 percent correlation with animal data due to the latter's natural variance, and so may *appear* inferior to animal tests due to the biological variability in the animal testing methods. In addition, human tissue-based in vitro methods may not show high correlation with animal tests because they correlate better with the human response – which is, after all, the ultimate goal. These discrepancies demonstrate not any inferiority of the in vitro alternative methods, but rather the scientific fallacy of animal test results as the standards of reference for such methods.

More than two dozen alternatives to animal tests have been validated by the European Centre for the Validation of Alternative Methods (ECVAM), and at least ten methods and deletions have gained regulatory acceptance to date in the EU. In the US, the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) has validated many fewer methods, clearly indicating a need for greater harmonization. This need is further illustrated by the favorable impact harmonization has had on reducing animal use in drug development and safety testing worldwide, by means of guidelines from the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and the Test Guidelines Program of the Organisation for Economic Cooperation and Development (OECD).

III. Current Practice: Costs and Problems Associated with Animal Use

Extrapolating research results across species is a tenuous enterprise. Animal test data are compromised by species differences in anatomy, organ structure and function, toxin metabolism, chemical and drug absorption, and mechanisms of DNA repair. These differences are compounded by additional variables related to experimental animal demographics and husbandry.

These problems manifest repeatedly when attempting to apply animal data to human diseases and drug responses. Examples include hormone replacement therapy for women, development of HIV protease inhibitors, Vioxx and other COX-2 inhibitors, teratology studies, harmful effects of smoking, non-steroidal anti-inflammatory drugs, antibiotics, antivirals, antidepressants, and cardiovascular medications, among others. Many harmful and ineffective drugs have tested safe and effective in animal studies. Conversely, many safe and beneficial human drugs would not survive animal testing today because of severe or lethal toxicities in some species.

Entire fields of translation science have demonstrated the failed paradigm of animal testing to predict human treatment responses. All of more than 80 preventive and therapeutic HIV/AIDS vaccines successful in nonhuman primates have failed in human trials. More than 4,000 studies have been reported demonstrating the efficacy of more than 700 treatments in animal models of stroke, yet none of the approximately 150 of these tested in humans has shown clinical benefit.

The entire field of cancer immunotherapy animal research has failed to produce even one successful therapeutic cancer vaccine. And dozens of human clinical trials have failed

due to toxicities or lack of efficacy after animal tests showed cures, mitigation, or prevention of diseases such as diabetes mellitus, spinal cord injury, multiple sclerosis, psychiatric disorders, and many others.

Ninety-two percent of drugs that enter clinical trials following extensive animal testing fail to achieve FDA approval for marketing, and this failure rate is at least 95 percent for cancer drugs. Of the eight percent overall that are approved, half are withdrawn or relabeled due to severe or lethal adverse effects not detected during animal testing. Levels of discordance between results from animals and humans range from 67 to 96 percent.

Recent examinations of animal trials have shown that they may occur concurrently or even after human studies, and the results are often conflicting; that there is poor correlation of cancer risk between assessments carried out by the US Environmental Protection Agency (EPA) and the International Agency for Research on Cancer (IARC); and that transgenic animal models frequently fail to duplicate human symptoms characteristic of many conditions, let alone enable scientists to elucidate the molecular processes underlying those diseases.

There are also economic advantages to replacement methods. For example, the DakDak test (used to measure the efficacy of sunscreens in preventing skin damage) can provide data for five or six products at less than half the cost of testing one product in animals. The current gold standard for testing a chemical to determine if it is carcinogenic is the rodent bioassay, which takes up to five years from planning to evaluation and review, at a cost of up to more than $4 million per substance. In vitro screening allows companies to identify promising test compounds in a cost- and time-efficient manner before progressing to expensive human trials.

Additionally, non-animal test methods save on various costs associated with animal methods, including animal procurement, maintenance and husbandry, and hazardous waste disposal. Finally, costly legal claims against companies that rely heavily on animal data may become more commonplace. For example, the pharmaceutical company Merck and Co., Inc. is currently facing litigation for alleged improper reliance on animal tests to show that its painkiller Vioxx was safe for humans.

Other factors resulting in the inherent suffering of animals used in testing include the manner in which animals are housed, transported and handled. Common laboratory routines have been shown to cause pronounced stress that can influence test results, and links between such stress and the development of behavioral stereotypies (which are believed to reflect animal suffering) are well established.

IV. Comparison of US and European Law

The potential for animals to suffer pain and distress in experiments was acknowledged in the US with the passage of the Animal Welfare Act (AWA) in 1966. Since its adoption, several amendments to the AWA, along with other supporting regulations and guidelines designed to improve the legal protection of animals in laboratories, have sought to reduce

animal suffering in research and testing, and have contributed to the promotion of non-animal alternatives to the use of animals in drug and product testing, research, and education.

Noteworthy in this regard is the 1993 National Institutes of Health Revitalization Act (NIHRA). This law calls for the NIH to "conduct or support research into methods of biomedical research and experimentation that do not require the use of animals," as well as for reducing the number of animals used in research. In 1997, the U.S. Congress established ICCVAM, comprising representatives from 15 federal agencies. ICCVAM's purpose is to conduct evaluations of new, revised and alternative test methods and to promote the scientific validation and regulatory acceptance of test methods that replace, reduce, or refine the use of animals.

Directive 86/609/EEC by the Council of the European Community is a primary factor responsible for Europe's pre-eminence in the field of non-animal methods, asserting that it is scientifically and morally insupportable to harm or kill animals when scientifically satisfactory alternatives are available. The EU Directive mandates the use of such non-animal methods, places their development and implementation into the political agenda of all EU countries, and has helped to spawn further legislation. The primacy of non-animal methods is largely accepted as the standard of practice by EU-based researchers and industry, but not yet by their American counterparts.

V. Support for this Petition

The American public is uncomfortable with animal experimentation and testing, particularly when it involves pain and distress or the testing of non-essential products. As a publicly funded agency, the FDA has a duty to use public monies in a cost-effective manner, and is obligated to address the concerns of the American public.

According to polls, 75 percent of Americans disapprove of animal experimentation and testing that cause severe pain and distress, and one-third object to all animal experimentation. Testing procedures account for the vast majority of animals reported in the highest categories of pain and distress, underscoring the importance of replacing animal use in regulatory toxicity testing. These prevailing sentiments suggest widespread public support for the goal of this petition: that replacement methods be *required* when they are available and proven scientifically satisfactory.

Broad scientific support for non-animal methods is demonstrated in the language drafted for adopted and proposed legislation, in the growth and diversification of such methods, and in the number of scientists and scientific organizations supporting them.

VI. Action Requested

The time is appropriate for regulatory and policy changes in the use of animals for preclinical drug and device testing. As long as FDA regulations and practices do not provide a mandate to achieve this, there is little incentive to change from the current

suboptimal preclinical testing methods. Requiring the use of humane and scientifically sound alternatives is vital to improve the accuracy of preclinical testing, minimize the approval of hazardous drugs and devices, decrease pain and suffering to animals, and advance the goal of replacing animal tests with more reliable and humane methods.

We request the FDA to promulgate a regulation to mandate that an animal experiment should not be performed if another *scientifically satisfactory** method for obtaining the result(s), not involving the use of animals, is available. The specific actions requested of the FDA are detailed in **Section A** of this petition.

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* *Scientifically satisfactory*: validated as an acceptable alternative to one or more animal tests currently in use, as evidenced by approval and enactment by any of the participant members of ICH (the US, the EU, and Japan), or by the FDA itself.

We further request that the FDA implement the objectives of the proposed regulation as follows:

A. The FDA should designate as *scientifically satisfactory* any and all methods validated as acceptable alternatives to one or more animal tests currently in use, as evidenced by approval and enactment by any of the participant members of ICH (the US, the EU, and Japan), or by the FDA itself.

B. The FDA should develop and implement standardized procedures requiring that its drug and device application reviewers accept as valid and sufficient any and all data submitted using scientifically satisfactory alternatives to animal test methods. Individual FDA reviewers must not require additional animal test data in such instances, or applicants will seek to include such data in initial applications so as to avoid approval delays.

C. The FDA should use the strongest possible language in its industry guidances regarding the acceptability and sufficiency of scientifically satisfactory non-animal alternatives, clearly indicating that the FDA requires only the non-animal data and does not require (and will not request) any animal test data thereby replaced.

D. The FDA should support efforts to obtain adequate funding directed specifically toward the development and utilization of its extensive human drug database as a particularly effective method for improving preclinical and clinical drug testing and public safety, informing FDA decisions regarding content of new drug or device applications, and replacing animal test methods with scientifically satisfactory non-animal alternative methods.