March 19th, 2015

Martin Schulz, President
and
Members of the European Parliament,
Brussels, Belgium

Re: Request to oppose the European Citizen's Initiative "Stop Vivisection"

Honorable President and Members of the European Parliament,

We strongly urge the European Parliament and Commission to oppose the "Stop Vivisection" Citizens' Initiative submitted in March 2015 that requests to abrogate the directive 2010/63/EU of the European Parliament and of the council of 22 September 2010 [1] and ban animal research. We support the existing directive 2010/63/EU that provides for ethical and justified use of animals for biomedical research while allowing the progress in scientific advances that have significantly benefited both human and veterinarian care. Adopting the initiative's proposal to stop animal research would have deleterious effects on the progress of medical research at a critical time when the research and medical communities are actively collaborating to find cures for devastating diseases that affect human beings of all ages. As a result, a ban on animal experimentation would:

(a) drastically halt our efforts to find better and safer treatments for both humans and animals under veterinarian care,
(b) put the unborn foetus, neonate, infant, child, and adult patients at unnecessary risk of harm by exposing them to chemicals that have not undergone safety and toxicology testing in animals,
(c) deprive investigators of model systems that can be used rigorously to obtain information on the effects of specific genes, signaling pathways, and candidate treatments within a live complex organism, and prepare the field for human experimentation.

We would like to specifically address the points raised in the "European's Citizens' Initiative – Stop Vivisection" (http://www.stopvivisection.eu) which do not accurately represent the reality.

Point 1: "there are solid scientific principles that invalidate the "animal model" for predicting human response; indeed, statistical analysis provides empirical evidence in support of this decision."
Animal studies have successfully predicted human responses in studies evaluating epilepsy drugs for their anticonvulsant effects. Specifically, the vast majority of antiepileptic drugs (~ 30) that are currently in clinical practice have been tested and validated in animal studies prior to entering clinical use. In the United States, the Anticonvulsant Screening Program (ASP) of the National Institutes of Health / National Institute of Animal models have allowed the Neurological Disorders and Stroke (NIH/NINDS), to successfully identify 9 drugs that are currently considered standards of care for people with seizures [2]. Of equal importance, many of these drugs identified through animal studies are also standards of care for animals that are under veterinarian care for epilepsy [3]. The continuing efforts to provide more effective antiepileptic drugs are of equal benefit to animals, that otherwise may face euthanasia due to frequent seizures [4].

We acknowledge that there is a vigorous and ongoing discussion on how to perform animal studies humanely, improve the predictive power of animal studies using the fewest number of subjects, and deliver better therapies. The International League Against Epilepsy (ILEA) has indeed formulated specific Task Forces (AES/ILAE Translational Research Task Force of the Neurobiology Commission of the ILAE) assigned to re-evaluate research strategies and optimize the way animal studies are done so that they can deliver better therapies. These discussions and efforts will further advance

our current drive to develop curative therapies, including for diseases that have no satisfactory treatments, and treatments that can improve the quality of life of those afflicted with seizures.

Point 2: "Animal experimentation can therefore be considered as posing a danger to human health and the environment"

Safety and toxicological studies in animals are required by regulatory bodies to ensure that candidate treatments under development do not have adverse effects that could harm patients or offspring of pregnant women who might have to be treated with them. There are no satisfactory alternatives. Although due to species differences, animal studies cannot predict all human potential adverse effects, animal testing has been able to predict 2/3 of toxic side effects seen in humans [5]. Animal safety / toxicology studies effectively filter out compounds that could cause serious side effects, including carcinogenesis, teratogenesis, cardiac toxicity, lethality, and cognitive impairment. Failure to meet these high regulatory safety and toxicology testing is indeed the number one reason that compounds do not enter clinical trials.

Point 3: "Animal experimentation can therefore be considered as constituting a hindrance to the development of new methods in biomedical research, based on the most recent scientific advances and an obstacle to taping into much more reliable, relevant, cheaper and more efficient research methods, provided by new technologies expressly conceived for humans."

In compliance with the directive 2010/63/EU of the European Parliament and of the council of 22 September 2010 [1], animal experimentation is done under the principle that it serves a purpose that cannot be addressed through the use of other models, such as computer models, in vitro studies, or studies in non sentient organisms. Computer models are valuable tools that predict effects on well-characterized cells but they cannot substitute for or predict the effects of a drug on networks of cells with the enormous complexity found in the human brain. Therefore, animal studies are currently irreplaceable. They do not hinder the use or development of other research tools and strategies, but rather complement their use so that the target mechanisms can be effectively studied within a more complex in vivo test system.

Point 4: "Urge the European Commission to abrogate directive 2010/63/EU "on the protection of animals used for scientific purposes" and put forward a new proposal aimed at phasing out the practice of animal experimentation, making compulsory the use - in biomedical and toxicological research - of data directly relevant for the human species."

We strongly urge the European Commission to vote against the recommendation to abrogate directive 2010/63/EU and phase out animal experimentation, because this would hinder efforts to develop therapies for potentially treatable diseases that significantly impact the quality of life of both human and animals. In epilepsy, a disease that affects 1% of the world population, animal experimentation is essential when we do not have any reasonable or better alternative for biomedical and toxicological research (in accordance with directive 2010/63/EU [1]). Justification for the purpose and necessity of animal experimentation is already routinely required in every animal protocol that researchers submit for approval prior to conducting these experiments. In many situations, human specimens or human experimentation cannot serve as an option. Specific examples in the field of Epilepsy include (but are not limited to) the following:

1) *Understanding the pathophysiology and developing therapies for pediatric and developmental disorders*: There are strict regulations for the testing of new candidate therapies in the pediatric human population, due to both safety concerns and issues about consenting very young individuals to be tested with drugs that could have life-long impact. The response of several pediatric epilepsy syndromes to drugs cannot be predicted by the response of older individuals to a new drug. A typical example is infantile spasms [6] a catastrophic and still poorly treated form of infantile epilepsy. In addition, several developmental disorders appear to involve injury to the developing brain during gestation, and may be due to drugs given to the pregnant mother. Using pregnant women to solve these issues and exposing the unborn fetuses to unknown risks of tested drugs would therefore be unethical. In these and many other similar settings, animal experimentation is necessary.
2) *Understanding the pathophysiology and developing therapies for rare conditions:* Many conditions (e.g., genetic disorders) are too rare to allow for rigorous clinical studies. The availability of animal models of such diseases has significantly advanced the field by providing experimental model systems to understand the pathogenesis and develop new treatments.
3) *Human specimens are not always feasible or ethical to obtain for research:* Although having living human tissue specimens for research would be ideal, this is usually not possible or ethical for brain diseases. Furthermore, these

specimens are of limited or very specialized nature, obtained strictly for diagnostic or treatment purposes (e.g., post-operatively) and usually when the disease is quite advanced. Often appropriate controls are not possible to obtain, rendering animal experimentation necessary.

Thank you for your kind consideration of this important matter.

Best regards,

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REFERENCES

1. DIRECTIVE 2010/63/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 22 September 2010 on the protection of animals used for scientific purposes. 2010. Available at: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32010L0063&from=EN. Accessed 3/16/15 2015.
2. ASP Working Group of the NANDS. The NIH/NINDS Anticonvulsant Screening Program (ASP): Recommendations from the working group's 2012 review of the Program. Epilepsia. 2012;53:1837-48.
3. Charalambous M, Brodbelt D, Volk HA. Treatment in canine epilepsy--a systematic review. BMC veterinary research. 2014;10:257.
4. Monteiro R, Adams V, Keys D, et al. Canine idiopathic epilepsy: prevalence, risk factors and outcome associated with cluster seizures and status epilepticus. The Journal of small animal practice. 2012;53:526-30.
5. Baillie TA, Rettie AE. Role of biotransformation in drug-induced toxicity: influence of intra- and inter-species differences in drug metabolism. Drug metabolism and pharmacokinetics. 2011;26:15-29.
6. Pellock JM, Hrachovy R, Shinnar S, et al. Infantile spasms: a U.S. consensus report. Epilepsia. 2010;51:2175-89.