August 8, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

PEOPLE FOR THE ETHICAL TREATMENT OF ANIMALS

HEADQUARTERS
501 FRONT STREET
NORFOLK, VA 23510
TEL 757-622-PETA
FAX 757-622-0457

RE: Docket No. FDA-2014-N-0189 and RIN 0910-AG38

To Whom It May Concern,

These comments on the Food and Drug Administration (FDA) Proposed Rule, *Deeming Tobacco Products to Be Subject to the Federal Food, Drug, and Cosmetic Act*, are submitted on behalf of People for the Ethical Treatment of Animals (PETA) and our more than three million members and supporters. PETA is committed to using the best available science to save animals from suffering in laboratory experiments and promote the acceptance of human-relevant methods for risk assessment.

In its proposed rule, FDA states that it does not have the authority to amend the February 15, 2007, reference date for predicate products with respect to e-cigarettes or other products. If this is the case, we are very concerned that manufacturers of newer proposed deemed tobacco products that are ineligible to enter the market through the substantial equivalence pathway will instead submit premarket tobacco applications (PMTAs). In its draft guidance for industry on PMTAs, FDA directs applicants to evaluate the toxicity, abuse liability, and carcinogenicity of their products using some combination of *in vitro*, *in vivo*, or *ex vivo* studies to demonstrate that they are appropriate for the protection of the public health. While we appreciate FDA's efforts to hold tobacco product manufacturers to this high standard, it is unconscionable that more animals be made to suffer and die in order to bring new tobacco products to market. We are also concerned by recent media reports that FDA is funding inhalation toxicity experiments on mice with e-cigarette vapor.

We note that the above description of the types of nonclinical studies that may be conducted to support PMTAs is nearly identical to that found in FDA's draft guidance on modified risk tobacco product applications (MRTPAs). Therefore, our previous comments on that draft guidance are broadly applicable. Those comments and supplementary comments on recent applications of nonanimal methods to toxicity testing of tobacco products are attached.

In our previous comments, we note that in its report *Scientific Standards for Studies on Modified Risk Tobacco Products*, the Institute of Medicine (IOM) recommends that the number of animal studies required to characterize an MRTP preclinically could potentially be reduced by setting composition standards or limits for certain

categories of MRTPs. In the proposed rule, FDA affirms that it has the authority to propose standards for proposed deemed tobacco products that are appropriate for the protection of the public health, including standards regarding additives, constituents, or other components. FDA also states that, in the case of products that contain fewer or substantially lower levels of toxicants, premarket applicants may not need to conduct any new nonclinical studies. With respect to e-cigarettes, FDA notes that some have advanced views that certain new non-combustible tobacco products, such as e-cigarettes, may be less hazardous than combustible products.

Therefore, we recommend that FDA set composition standards for e-cigarettes and, more specifically, e-liquids. These standards should include a list of pre-approved ingredients (e.g., vegetable glycerin, propylene glycol, flavorants, and nicotine). If manufacturers use only pre-approved ingredients, then their PMTAs should be eligible for approval without conducting new nonclinical studies.

Setting such standards for e-liquids would seem to benefit all stakeholders. In the proposed rule, FDA expresses concern over contamination and variation in nicotine content of e-liquids as well as the long-term effects of flavored tobacco product usage. FDA also acknowledges that the proposed rule would have a significant economic impact on a substantial number of small entities and notes that it is collecting information on how it can streamline the review of new product applications. Composition standards for e-liquids would enable FDA to address its concerns proactively and reduce the review process to a matter of assuring compliance for many PMTAs. It would also establish a regulatory framework in which small manufacturers could continue to thrive, free of burdensome testing requirements. In this regard, we note that essentially identical recommendations have been submitted independently by at least two such manufacturers—The Vaporist, LLC, and Republic Tobacco, LP—indicating that similarly positioned manufacturers would likely be receptive to such an approach. Our communications with e-liquid manufacturers also indicate broad opposition to conducting animal tests of their products.

The FDA expresses concern that e-cigarettes are being marketed with characterizing flavors that can be especially attractive to youth and notes that the Tobacco Control Act prohibits such flavors in cigarettes only. Determining that e-cigarettes are cigarettes with respect to this prohibition, along with setting composition standards, as described above, could further simplify the proposed regulatory framework. Our review of comments already submitted indicates that e-cigarette and e-liquid manufacturers are divided on this issue. As suggested by the Consumer Advocates for Smoke-free Alternatives Association (CASAA), a compromise is to regulate inexpensive, widely distributed cigarette look-alike products as conventional cigarettes while exempting e-liquids and the more expensive refillable devices in which they are used. CASAA notes that, like premium cigars, such products are used mainly by adult connoisseurs and can generally only be found in specialty stores. Both of these options address FDA’s concerns while avoiding additional testing requirements.

The FDA's statement that, in the case of products that contain fewer or substantially lower levels of toxicants, premarket applicants may not need to conduct any new nonclinical studies is at odds with recent media reports that it is funding inhalation toxicity experiments on mice with e-cigarette vapor. While FDA cites recent studies suggesting that e-cigarettes may have the potential to substantially reduce exposure to tobacco-specific toxicants and help with smoking cessation, it ultimately concludes that it does not have sufficient data to determine what effects e-cigarettes have on the public health. However, considering the physiological difference between species and the failure of animal experiments to predict the adverse health effects of tobacco exposure in humans, it is unlikely that useful data will be obtained from these experiments. Many of the nonanimal methods reviewed in our supplementary comments on FDA's draft guidance on MRTPAs are applicable to the study of e-cigarette vapor. These include methods to evaluate cytotoxicity, apoptosis, genotoxicity, and inflammation that are among the *in vitro* assays that IOM identified as a standard step in the evaluation of all tobacco products—which should precede any *in vivo* studies. FDA must encourage tobacco product manufacturers to heed these recommendations by both revising its draft guidance to industry and funding only human-relevant, nonanimal research.

Thank you for your attention to these comments. I can be reached at 757-622-7382, ext. 8001, or via e-mail at JosephM@peta.org.

Sincerely,

Joseph Manuppello, M.Sc.
Senior Research Associate
Regulatory Testing Division
People for the Ethical Treatment of Animals