January 4, 2018

Caryn Cohen
Office of Science
Center for Tobacco Products (CTP)
Food and Drug Administration (FDA)
Document Control Center
Bldg. 71, Rm. G335
10903 New Hampshire Ave.
Silver Spring, MD 20993–0002

PEOPLE FOR
THE ETHICAL
TREATMENT
OF ANIMALS

Washington, D.C.
1536 16th St. N.W.
Washington, DC 20036
202-483-PETA

Los Angeles
2154 W. Sunset Blvd.
Los Angeles, CA 90026
323-644-PETA

Norfolk
501 Front St.
Norfolk, VA 23510
757-622-PETA

Oakland
554 Grand Ave.
Oakland, CA 94610
510-763-PETA

Info@peta.org
PETA.org

Dear Ms. Cohen,

On behalf of our more than six million members and supporters, People for the Ethical Treatment of Animals (PETA) thanks the Tobacco Products Scientific Advisory Committee for the opportunity to comment on modified risk tobacco product (MRTP) applications submitted by Philip Morris Products S.A. (PMP S.A.) for its IQOS system with Marlboro Heatsticks. PETA is committed to using the best available science to save animals from suffering in regulatory testing and protect public health and the environment.

PETA's interest in tobacco product marketing applications is that no more animals be made to suffer and die in order to bring new tobacco products to market. While we understand the principle of "continuum of risk", tobacco use is ultimately a personal choice. Whatever one's opinion on animal use, harming animals in attempts to make our needless and ill-considered choices less risky is surely unjustified. **We ask TPSAC to clearly state that no more animals should be used to test the IQOS system and its components. In addition, we ask TPSAC to call in data on earlier versions of the IQOS products and request that PMP S.A. update its application in order to verify that the chemical characterization and standard *in vitro* tests of the IQOS aerosol were completed before *in vivo* tests were considered.**

In its application, PMP S.A. reports results of three animal experiments: two 90-day inhalation toxicity tests and one systems biology study. These experiments used more than 400 animals. The inhalation tests employed nose-only exposure, in which rats were immobilized in glass tubes only slightly larger than their bodies, connected to an inhalation chamber, and exposed to test substances for six hours each day for as long as 137 days or about 20% of their life-spans. For the systems biology study, mice were exposed whole-body for eight months. It must be noted that the reported tests are for IQOS products only – an even greater number of animals was used in tests of earlier versions of these products.

For a 2011 FDA workshop on the scientific evaluation of MRTP applications, Altria Client Services submitted an extensive assessment of one of these earlier versions, an Electrically Heated Cigarette Smoking System (EHCSS), which was completed by Philip Morris USA in 2006. These experiments used approximately1,100 mice and rats, including 650 mice for a skin-painting experiment. At the same time, routine chemical analysis revealed that the concentration of formaldehyde from EHCSS aerosol was approximately sevenfold greater than that from reference combustible

Affiliates:
- PETA Asia
- PETA India
- PETA France
- PETA Australia
- PETA Germany
- PETA Netherlands
- PETA Foundation (U.K.)

cigarettes. In a meeting with CTP in 2013, I cited this as an example of tobacco product manufacturers using the results of animal tests to understate the known risks of their products, a strategy which these companies employed for decades with combustible cigarettes.

In its application, PMP S.A. also reports the results of three *in vitro* toxicity tests and five *in vitro* systems biology studies. In previous comments, we have noted that these researchers pioneered the use of reconstituted human bronchial epithelium, exposed to whole smoke at the air-liquid interface, to measure perturbations in biological pathways. More recently, these researchers have developed a framework for the *in vitro* systems toxicology assessment of e-liquids.[1] This physiologically relevant approach seems to embody the National Research Council's vision for transforming toxicology from an observational to a predictive science, and we are grateful for these broadly applicable accomplishments. We sincerely hope that PMP S.A. will continue to support and expand these efforts.

PMP S.A. reports the results of eight clinical studies with smokers. The results of these studies consistently showed that exposure to IQOS aerosol produced significantly less toxicity and fewer adverse effects than exposure to cigarette smoke and did not introduce new or increased risks. Such clinical studies will always be needed in order to support MRTP applications. As the Institute of Medicine (IOM) correctly observed in its report, *Scientific Standards for Studies on Modified Risk Tobacco Products*, preclinical assays alone are "fundamentally incapable" of demonstrating that new tobacco products are less risky than existing ones. IOM concluded that the role of preclinical assays is to identify particularly risky products that should not be tested in humans as well as products that have a reasonable potential to reduce risk. As these goals have already been attained for IQOS products, there can be no justification for additional animal tests.

IOM also recommended that "[e]valuation of products *in vitro* should precede *in vivo* assays." From the materials currently available, it is unclear whether this was the case for the reported tests. In its summary, PMP S.A. should include a timeline showing when these tests were conducted in order to verify that the chemical characterization of the IQOS aerosol and standard *in vitro* tests were completed before *in vivo* tests were considered. Further, as we have suggested in previous public comments, the need for this information should be stated in FDA's guidance to industry and TPSAC should request it for its review of these, and subsequent, MRTP applications.

Thank you for your attention to these comments. I can be reached at 757-793-8941 or via e-mail at JosephM@peta.org.

Sincerely,

Joseph Manuppello, M.Sc.
Senior Research Associate
Regulatory Testing Department

[1] Iskandar AR, et al. A framework for in vitro systems toxicology assessment of e-liquids. *Toxicol Mech Methods*. 2016;26:389–413.