June 4, 2012

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

RE: Docket Identification Number FDA–2012–D–0071

These comments on the Food and Drug Administration’s (FDA) Draft Guidance for Industry: Modified Risk Tobacco Product (MRTP) Applications (Draft Guidance) are submitted on behalf of PCRM. PCRM is a nonprofit 501c3 organization headquartered in Washington, D.C., and since 1985 has been an advocate for preventive medicine, especially good nutrition, and higher ethical standards in research. Our membership includes more than 125,000 health care professionals and concerned citizens.

In its Draft Guidance, FDA recommends that industry use a variety of nonclinical and clinical studies in order to provide information in its application to allow FDA to determine whether it can issue “risk modification” or “exposure modification” orders to allow industry to market products as MRTPs, including in vivo animal studies. While we acknowledge that this guidance is “non-binding” and does not constitute testing requirements per se, we must point out that if industry would like to apply for an order, it essentially should conduct the studies that FDA (and the Institute of Medicine) recommend. Like the FDA’s guidance for other products, animal studies become implied or default requirements. This guidance is problematic because it recommends certain in vivo animal studies, and simultaneously does not offer suggestions on how to implement minimal “3Rs” or replacement, reduction, and refinement practices within industry’s MRTP testing programs. Therefore, we would like the FDA to remove recommendations for in vivo animal studies from this guidance. Such a precedent is supported internationally.\(^1\)\(^,\)\(^2\)

Because of the well-known and understood risks of tobacco products to users and often even non-users, there is a very high bar to be met to certify any products as modified risk. This bar cannot be met using animal studies. Human-relevant in vitro and clinical investigations must be conducted, as indicated in the Draft Guidance. Historically, the


testing of tobacco products on animals has at best failed to offer clarity in determining the risks of such products to humans, and at worst misled companies and assessors, providing irrelevant or incorrect information.\textsuperscript{3,4,5,6} There is no reason to believe differently in this case.

The FDA recommends that in order to assess the comparative “abuse liability” of MRTPs, “animal models of conditioned place preference (CPP), drug discrimination and self-administration” may be used. There are questions within the psychological and drug abuse literature as to the applicability of these types of studies to nicotine (as opposed to other drugs) and to humans (interspecies extrapolation). Because of the uncertainties inherent in these approaches, relying on animals to predict the relative addictive potential of tobacco products risks certifying more addictive products as MRTPs.

CPP studies have a number of limitations, including apparatus preference bias, handling stress, and novelty seeking effects. There is debate over whether the results obtained from CPP studies can be extrapolated to humans. Some claim that since the animal passively receives the drug, it is of limited usefulness.\textsuperscript{7,8}

The Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) of the European Commission indicates that the “…abuse liability of pure nicotine [in animal self-administration studies] is weaker than the addictive potential of tobacco products in humans.” Also, there is much disagreement about whether neurobiological addiction processes seen in animals in laboratory studies is applicable to humans.\textsuperscript{9}

Because final determinations regarding the potential reductions in risk to users and non-users rely so much on human behavior and the whole experience of product use (e.g., packaging, advertisements, perception of risk), it is essential to mimic the real-world

\textsuperscript{3} Coggins C. A further review of inhalation studies with cigarette smoke and lung cancer in experimental animals, including transgenic mice. Inhal Toxicol. 2010 Oct;22(12):974-83.


\textsuperscript{6} Coggins C. A minireview of chronic animal inhalation studies with mainstream cigarette smoke. Inhal Toxicol. 2002 Oct;14(10):991-1002.


situation as far as possible. However, many addiction studies inject animals with nicotine, limiting clear extrapolation to the human experience. Obviously, it is also not possible to assess other preference or behavior factors using animals. On the other hand, clinical studies with human volunteers can be used to assess these factors,\textsuperscript{10} and chemical studies as well as receptor docking and other in vitro assays can be used to discriminate between the biochemical properties of nicotine and other similar compounds.\textsuperscript{11}

In conclusion, using animal studies to assess MRTPs, even as one piece of a weight-of-evidence approach, has the potential to introduce misleading evidence into the assessment and should not be recommended. The use of animals for studies of addiction potential is unethical because of dubious validity and unclear links to actual human addiction and behavior. The potential for reductions in risk to tobacco product users, and benefits to public health as a whole, should be assessed using human-relevant \textit{in vitro} and clinical studies.

Thank you for your attention to these comments. I can be reached at ksullivan@pcrm.org or by phone at 1-510-923-9446.

Sincerely,

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