American Enterprise Institute for Public Policy Research
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Scott Gottlieb, M.D.
Commissioner
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

November 7, 2017

Re: Docket No. FDA-2017-D-3001, Modified Risk Tobacco Product Applications: Applications for iQOS System With Marlboro Heatsticks, iQOS System With Marlboro Smooth Menthol Heatsticks, and iQOS System With Marlboro Fresh Menthol Heatsticks Submitted by Philip Morris Products S.A.

Dear Dr. Gottlieb:

We are scholars at the American Enterprise Institute, a nonpartisan, nonprofit policy research entity. Dr. Satel is a practicing psychiatrist who has studied and researched a broad range of matters related to mental health policy and addiction, including tobacco harm reduction. Mr. Brill is an expert in public finance and health economics, with a concentration in the economic and public health implications of smoking and its alternatives. The views expressed here are ours alone and may or may not reflect the views of our colleagues.

Thank you for the opportunity to comment on the modified risk tobacco product (MRTP) applications by Philip Morris Products S.A. cited above under section 911(g) of the Federal Food, Drug and Cosmetic Act. Philip Morris is seeking approval to make specific claims about risks of its heat-not-burn (HNB) technology (commercially known as iQOS) relative to conventional cigarettes. We urge the FDA to expeditiously review these applications and permit the sale and marketing of iQOS to American consumers.

Important Differences Between HNB and Combustible Tobacco Products

Adverse health consequences of combustible tobacco products are significant, and all strategies intended to reduce smoking should be considered. Though smoking among US adults is at a historic low, roughly 36.5 million engaged in the practice in 2015 (CDC, 2016). Smoking remains the most preventable cause of premature death. Smoking-attributable mortality has been estimated at 480,000 annually (CDC, 2014). Healthcare costs associated with cigarette smoking have been estimated at $167 billion annually, with half of that cost being borne by Medicaid and Medicare and $24 billion incurred by other federal programs (Xu, 2014).

The products of combustion of tobacco, such as tar and other toxins and gases, are the overwhelming source of carcinogens and the cause of hypertension, lung disease, and cardiovascular pathology associated with smoking. In general, tobacco products that do not involve combustion are less hazardous than those that burn tobacco leaves. Because iQOS heats but does not burn tobacco, it does not impose health risks comparable to traditional combustible tobacco products. Its reduced risk technology uses a blade to heat compressed tobacco that comes in the form of a stick that is inserted into a battery-powered device. The tobacco stick is heated to a maximum of 662 degrees Fahrenheit, well below combustion temperature of about 1300 degrees Fahrenheit.

In our view, it is imperative that current US smokers have access to and be properly informed about safer options. This is closely aligned with the new FDA commitment to regulate nicotine and tobacco products according to a continuum of risk.

Scientific Evidence on Relative Risk of HNB Technology

Toxicology Data

Toxicological data to date strongly suggest that iQOS HNB technology delivers enough nicotine to function as an alternative to smoking, and the low carbon monoxide concentration confirms that no combustion is taking place. The significant reductions in other various toxins strongly imply a reduced relative risk of this product class relative to an ordinary cigarette. Examples of these findings include the following.

A 2017 study of iQOS by the Japanese National Institute of Public Health examined the nicotine concentration in the tobacco "heat stick" and mainstream aerosol of iQOS relative to conventional cigarettes and found concentration of nicotine in both tobacco filler and mainstream smoke to be comparable, but the level of tobacco-specific nitrosamines and the level of carbon monoxide was one-fifth and one-hundredth, respectively, the level in cigarette smoke.

At the recent 2017 Global Forum on Nicotine, cardiologist and clinical researcher Konstantinos Farsalinos reported data, now in press, on iQOS toxic emissions. His research finds an average reduction of 90 percent for 37 harmful and potentially harmful contaminants compared to reference cigarettes. In particular, toxins such as carbon monoxide, toluene, and isoprene measured under 5 percent in iQOS relative to a reference cigarette; N-nitrosonornicotine (NNN), around 5 percent; phenol and formaldehyde, around 10 percent; and acetaldehyde and acrylamide, 30–40 percent.

Clinical Evidence

Clinically, risk reduction has been demonstrated in an open-label study by Philip Morris researchers. Smokers were given ad libitum access to an HNB device for five days in an "inpatient" setting and were followed for 86 days. Trials were carried out in the US and in Japan with subjects who were not planning on quitting within the next six months.

Results show that smokers who switched to the HNB technology inhaled reduced levels of 15 harmful chemicals compared to smokers who continued to smoke.

Another clinical study investigated the effect of switching from conventional cigarettes to HNB technology in Japanese smokers. One hundred sixty participants were randomized to HNB technology, combustible cigarettes, or smoking abstinence for 5 days in confinement and 85 days in an ambulatory setting. Endpoints included biomarkers of exposure to harmful or potentially harmful constituents (HPHCs) and clinically relevant risk markers of oxidative stress, platelet activation, endothelial function, and lipid metabolism. In terms of lung function, forced expiratory volume in one second was measured. Across measures, changes in the group assigned to HNB approached those in the abstinence group.

In sum, evidence derived from short-term clinical investigations also strongly indicates a reduced risk profile for HNB products relative to cigarettes. Furthermore, ecological data suggest that iQOS is appealing to smokers. Each heat stick provides 12–14 puffs per stick over the course of around six minutes, the typical time and puff amount of an average cigarette. The use of real leaf tobacco yields a sensory experience that is more like smoking, an advantage to smokers who want a safer way to consume tobacco and nicotine. In Japan, for example, where other reduced risk products (e.g., smokeless tobacco and nicotine-containing vaping products) are effectively unavailable, between 60 and 70 percent of smokers who have tried iQOS have fully converted.

Conclusion

The FDA's Center for Tobacco Products (CTP) has a clear and appropriate mission statement: "To protect Americans from tobacco-related death and disease by regulating the manufacture, distribution, and marketing of tobacco products and by educating the public, especially young people, about tobacco products and the dangers their use poses to themselves and others."

HNB devices, such as iQOS, do not combust tobacco, and a large body of scientific evidence demonstrates that such devices produce similar amounts of nicotine but greatly reduced amounts of HPHCs. For this reason, there is diminished risk associated with these products relative to traditional cigarette products.

Consistent with the CTP's mission and its objective of improving public health by reducing preventable death, HNB technology offers valuable benefit for current smokers. Access to these less-risky products along with reliable, fact-based evidence on the relative risks is vital for today's smokers.

Thank you for the opportunity to provide comments regarding the MRTP applications for iQOS systems. We urge the FDA to approve these applications and proceed in an open and transparent manner so that additional manufacturers can also receive timely consideration. We would be happy to answer any questions you may have. Dr. Satel can

be contacted at slsatel@gmail.com or 202-489-6654, and Mr. Brill is available at alex.brill@aei.org or 202-862-5931.

Sincerely,

Alex Brill	Sally Satel, M.D.
Resident Fellow	Resident Scholar