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Feb. 1, 2020

Docket No. FDA-2017-D-3001-0002
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket No. FDA-2017-D-3001-0002 for Modified Risk Tobacco Product 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 Commissioner Hahn,

I write to you on behalf of the R Street Institute, a Washington-based nonprofit, nonpartisan, public policy research organization dedicated to free markets and real solutions. Exploring ways that tobacco harm reduction strategies could address the thousands of smoking-related deaths that the United States continues to experience annually has been a major focus of R Street research since the institute opened its doors eight years ago. It is in light of that prior research that we provide this update to our support of the Modified Risk Tobacco Product request for the IQOS system and urge the Food and Drug Administration to approve this application.

The addition of "Response to the FDA's Request for Information of November 20, 2019 for MR0000059-MR0000061 and MR0000133" to the MRTP application materials responds to study results from mouse models of lung cancer used to justify the IQOS system's relative risk compared to combustible cigarettes. The data the applicant presents in response to the FDA's request for information offers strong evidence that the observed differences in mortality rates between IQOS aerosol-exposed male A/J mice and control (i.e., "sham") air-exposed mice are largely due to intrinsic characteristics of A/J mice.

A/J mice are genetically susceptible to tumor development, a trait perpetuated through long-term brother-sister mating.[1] The side effect of this inbreeding is susceptibility to several other health problems

[1] "Mouse Strain Datasheet – 000646," The Jackson Laboratory, accessed January 28, 2020. https://www.jax.org/strain/000646.

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and decreased life span, which happen to be more evident in males.[2] An intrinsic limitation of using this mouse model is that some natural variability in those traits may exist in the sample population. Litter-to-litter differences can also bias results in mouse models.[3] Examining the causes of mortality between the male high IQOS aerosol-exposed mice and the controls (Figure 5 and Table 4) shows that the distribution of causes of early death is vastly different among the male, high IQOS aerosol-exposed mice from the other groups, including the controls. Although the exposed group had twice the number of early deaths, compared to the control mice, the exposed group experienced half the number of neoplasms. Also, the first early death caused by neoplasms among the exposed group occurred 120 days after the first death from neoplasm among the control group. These results suggest that carcinogens from exposure to IQOS aerosol are not the cause of the observed differences in early mortality between these groups of male mice.

The Kaplan-Meier curve for male, high IQOS aerosol-exposed mice compared to controls also shows that the survival rate for the exposed mice begins decreasing sharply, causing clear divergence from the control group, around day 260, with the curves becoming more parallel (indicating that the two groups are experiencing early deaths at roughly the same rate) somewhere between day 360 and 390 (Figure 4). Referencing Figure 9—the Kaplan-Meier curve for male, high IQOS aerosol-exposed mice by major cause of mortality—only one death from neoplasms occurs between days 260 and 360, whereas roughly half of the early deaths due to impairment of the urogenital tract and unknown causes occur during the same period. This also suggests that the divergence in the survival rates between these two groups is attributable to causes other than tumors, one of which is a known genetic vulnerability in the A/J mouse strain.[4]

Taking the full body of evidence into consideration, the observed differences in mortality rates between IQOS aerosol-exposed male A/J mice and control mice appear to be the effect of an unknown variable(s), which is likely the result of an unidentified congenital abnormality among A/J mice. The results addressed in the applicant's response vary considerably from the other results presented in its MRTP application, strongly suggesting the aberration in results is due to noise or residual confounding. As such, these results should not overwhelm the full body of evidence presented in support of the IQOS system's MRTP application.

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[2] Ibid.
[3] Stanley E Lazic and Laurent Essioux, "Improving basic and translational science by accounting for litter-to-litter variation in animal models," *BMC Neuroscience* 14:37 (2013). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3661356.
[4] "Mouse Strain Datasheet – 000646." https://www.jax.org/strain/000646.

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Sincerely,

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