PHILIP MORRIS
PRODUCTS S.A.

August 30, 2018

Benjamin Apelberg, Ph.D.
Director
Division of Population Health Science
Office of Science
Center for Tobacco Products
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Submitted via External Drive

Re: Amendment to MR0000059-MR0000061 - Additional information

Dear Dr. Apelberg,

We hereby provide, in amendment to the above mentioned Modified Risk Tobacco Product applications, results of the recently finalized *in vivo* study "*Lung cancer tumorigenesis in A/J mice in response to 18 months of chronic exposure to mainstream aerosol from THS 2.2 versus smoke from conventional cigarettes*" (Study 15020 - A/J mice lung cancer study). This submission follows the timelines recently communicated by PMP S.A. in a teleconference organized by FDA on July 18, 2018, which was further confirmed in the latest response to the Agency's Advice/Information Request on August 3, 2018 (response to Question 4).

This evidence package summarizes results of an 18-month combined chronic toxicity and carcinogenicity study in A/J mice. It describes the impact of THS exposure on lung inflammation, emphysema and lung carcinogenesis in comparison with cigarette smoke. The study results are remarkably consistent with those of our previous THS assessment studies and provide further evidence that the carcinogenic potential of THS aerosol is significantly lower than that of cigarette smoke.

To complete the evidence package on disease risk reduction of THS, the *in vivo* A/J mice lung cancer study is complemented by two *in vitro* studies: Ames bacterial reversion test investigating mutagenicity and Micronucleus assay investigating genotoxicity of the THS aerosol.

The Ames bacterial reversion test was conducted to investigate mutagenicity of the mainstream Gas Vapor Phase (GVP) aerosol fractions generated with THS. This study was performed in addition to the *in vitro* study investigating mutagenicity of the Total Particulate Matter (TPM) derived from the aerosol fractions generated with THS, which was provided as part of our initial submission. The results of the Ames test revealed that GVP, similarly to the TPM, was not mutagenic.

The *in vitro* Micronucleus assay was conducted to investigate genotoxicity of the mainstream GVP aerosol fractions generated with THS. The study results indicate that TPM and GVP derived from *HestSticks* have lower (between 7.7 - 15.1 fold) *in vitro* genotoxic potency compared to respective fractions from the 3R4F reference cigarette.

This amendment contains confidential commercial and/or trade secret information. Protection of this information from public disclosure is hereby claimed under the applicable provisions of United States law. We request the Agency to provide pre-disclosure notification and follow the procedures in 21 C.F.R. §20.61(e) before publicly disclosing any information contained in this amendment.

We remain available for any further information that is required.

Sincerely,

Malgorzata Wronowska, PhD
Director Regulatory and Scientific Affairs
Philip Morris Products S.A.

Jeffrey Walker, M.D.
US Agent for PMP S.A.
CEO, Teton Regulatory Sciences

Enclosures: Appendix A