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Philip Morris International
Summary of Modified Risk Tobacco Product Application
Submitted to U.S. FDA on December 5, 2016

Introduction

Philip Morris International (PMI) submitted a Modified Risk Tobacco Product Application (MRTPA) to U.S. Food and Drug Administration for its novel Tobacco Heating System (THS)[1] with three different tobacco consumables, Marlboro *HeatSticks*, Marlboro Smooth Menthol *HeatSticks*, and Marlboro Fresh Menthol *HeatSticks*.

THS is a patented novel tobacco product with three components: a tobacco stick, a holder and a charger.

THS is fundamentally different from a combustible cigarette; the system has been designed to heat tobacco without burning it. PMI is currently selling THS in several countries, including Japan, Switzerland and the UK. Over 2 million adult smokers have switched fully from cigarettes to THS.

Under Section 911 of the *Family Smoking Prevention and Tobacco Control Act* (Tobacco Control Act), signed into law in 2009, manufacturers can submit applications for FDA authorization to market tobacco products with claims of either reduced risk or reduced exposure (Modified Risk Tobacco Products; MRTPs). Such applications must be supported by adequate scientific evidence as detailed in the Tobacco Control Act.

PMI's Modified Risk Tobacco Product Application seeks FDA's authorization for the following label and marketing statements:

- Statement 1 (Section 911(g)(1)):
  - The [THS] system heats tobacco but does not burn it.
  - This significantly reduces the production of harmful and potentially harmful chemicals.
  - Scientific studies have shown that switching completely from cigarettes to the [THS] system can reduce the risks of tobacco-related diseases.
- Statement 2 (Section 911(g)(1)):
  - The [THS] system heats tobacco but does not burn it.
  - This significantly reduces the production of harmful and potentially harmful chemicals.

[1] THS is commercially marketed outside the US as IQOS. This product is not available for purchase in the U.S.

    - Switching completely to [THS] presents less risk of harm than continuing to smoke cigarettes.
- Statement 3 (Section 911(g)(2)):
    - The [THS] system heats tobacco but does not burn it.
    - This significantly reduces the production of harmful and potentially harmful chemicals.
    - Switching completely from cigarettes to the [THS] system significantly reduces your body's exposure to harmful and potentially harmful chemicals.

PMI's MRTPA provides results from its extensive program of rigorous scientific studies (Smith 2016) on THS to support these claims. The results cover the potential risk reduction and exposure reduction benefits of THS, as well as the likely impact of marketing the THS system on population harm. The evidence on population harm addresses, among other things, the likelihood of THS to decrease prevalence of cigarette smoking among current smokers, as well as its likely effect on tobacco use among never and former smokers.

Background

Cigarette smoking causes serious and fatal diseases, including heart disease, lung cancer, and chronic obstructive pulmonary disease (COPD). It is well known that the best way to prevent the harms of smoking is never to start and, for smokers, to quit. For decades, therefore, public health advocates and governments have focused on prevention and cessation in developing policies to reduce the harm caused by smoking. However, although the smoking prevalence has declined from 21% to 17% over the last decade, an estimated 40 million people currently smoke cigarettes in the United States (CDC 2015).

Smoking-related harm and disease are directly caused by the long-term exposure to the toxicants found in smoke from combustible tobacco products (HHS 2010). In conventional cigarettes, the lit end can reach temperatures in excess of 1600 °F. Such high temperatures cause a large number of chemical reactions to take place, breaking down the tobacco into the chemicals that appear in cigarette smoke. Public health authorities have classified some of those smoke constituents as likely causes of smoking-related diseases such as lung cancer, heart disease and emphysema. FDA refers these constituents as *harmful or potentially harmful constituents (*HPHCs*)*.

It is widely recognized that '*most of the harm caused by smoking arises not from nicotine but from other components of tobacco smoke*' (Royal College of Physicians 2016). For instance, '*FDA believes that the inhalation of nicotine (i.e. nicotine without the products of combustion) is of less risk to the user than the inhalation of nicotine delivered by smoke from combusted tobacco products.*' (FDA 2016).

If tobacco is instead heated to temperatures of around 700°F or lower, an aerosol is produced that is not the product of combustion. At these temperatures, many of the chemical reactions associated with combustion do not to take place. THS was designed to avoid combustion, and instead generate an aerosol, expected to produce significantly lower levels of toxicants than cigarette smoke. The key to THS's potential for reduced toxicity is the reduced formation of HPHCs, compared to the HPHCs created primarily through combustion in cigarettes.

While eliminating combustion to reduce toxicants is crucial, MRTPs must also be acceptable and appealing to adult smokers so that they will actually use them and switch completely from cigarettes. As Dr. Ernst Wynder, a leading epidemiologist and pioneer in smoking and health research, stated in 1979 (quoted in IOM 2001), *"…it is important to appreciate that a virtually harmless [tobacco product used] by only 1% of*

the population will have a lesser impact on the reduction of tobacco-related diseases than a somewhat more harmful [product used] by 80% of the total smoking population." In fact, a product with less harm but with low appeal is unlikely to generate public health benefits.

The following simple equation illustrates the point that population harm reduction depends on both the availability of significantly lower risk products and a significant number of adult smokers willing to accept and switch to these products. Furthermore, as MRTPs are not risk-free, these products should not attract persons who do not currently use tobacco products, i.e. never-smokers or former smokers.

In addition to reducing the formation of HPHCs, PMI sought to maintain appeal to, and acceptance of, THS by adult smokers by replicating, insofar as possible, the taste, nicotine delivery and ritual characteristics of cigarettes. Nicotine is important because nicotine delivery profile and rewarding subjective effects are critical components of product satisfaction and actual use, which are key to switching. Further, public health authorities acknowledge that while addictive and not risk free (and thus not appropriate for, among others, youth, pregnant women and nonsmokers), nicotine is not the primary cause of smoking-related disease.

PMI's Application

Under Section 911(g)(1) of the Tobacco Control Act FDA will issue a modified risk marketing order for a tobacco product if the applicant satisfies a two-part "basis for approval". The applicant must demonstrate that the product "*as it is actually used by consumers, will (a) significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and (b) benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products*."

Section 911(g)(2) permits manufacturers to apply for authorization for a claim of reduced exposure. FDA will issue a modified risk marketing order if the applicant satisfies a number of requirements, including that such product would be appropriate to promote public health, the magnitude in exposure reduction is substantial, and the product is reasonably likely to lead to reduction in overall morbidity and mortality among individual tobacco users.

Smoking-related harm and disease are directly caused by the long-term exposure to the toxicants found in smoke from combusted tobacco (HHS 2010). Consequently, smoking cessation is the most effective way to reduce the harm and risk of tobacco-related disease. This is because cessation eliminates the exposure to the HPHCs contained in the smoke. Smoking cessation has therefore been referred to as the "gold standard" for the assessment of candidate MRTPs such as THS (IOM 2012). Based on these principles, the assessment of THS needs to demonstrate that switching to THS leads to a reduction in exposure to HPHCs, which in turn leads to a significant reduction in harm.

With these principles in mind, PMI established its multistep THS assessment program applying internationally accepted scientific and quality standards (Smith 2016). The MRTPA provides a detailed mapping of that process, showing how PMI developed studies to address the statutory requirements and

FDA's Draft Guidance for Industry for Modified Risk Tobacco Product Applications using internationally accepted toxicity tests, advanced systems toxicology methods, clinical studies as well as innovative perception and behavior studies. Importantly, PMI's MRTPA addresses the two-part "basis for approval" allowing FDA to assess the impact of marketing THS with claims in the U.S.

The MRTPA provides the following evidence:

- Product design and control principles:
  PMI's processes and practices ensure that the product meets quality standards and specified performance parameters, including product design principles, manufacturing quality controls and a change management process. The processes and related data establish that THS heats tobacco at controlled temperatures below those needed for tobacco to burn and that there is no combustion.

Part A: "*The product, as it is actually used by consumers, will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users.*"

- Aerosol chemistry and physics:
  PMI conducted thorough scientific studies to assess the THS aerosol chemistry (HPHC formation), aerosol physics and indoor air chemistry. The data demonstrated that the aerosol generated by THS had levels of HPHCs that on average were 90 to 95% lower than those measured in the smoke of a 3R4F research cigarette. In addition, the THS aerosol did not negatively affect indoor air quality.

    - PMI measured 54 HPHCs, which includes the 18 HPHCs FDA requires manufacturers to quantify and report to FDA. The levels of these HPHCs, excluding nicotine, were on average 90% lower than those measured in the smoke from the 3R4F reference cigarette (Schaller 2016). Similarly, the levels of 15 chemicals classified by the International Agency for Research on Cancer (IARC) as Group 1 carcinogens were reduced on average by more than 95% compared to a reference cigarette.

    - Indoor air chemistry studies were conducted to determine the concentrations of 18 different analytes under standardized indoor environmental conditions (residential, office, hospitality). Only nicotine and acetaldehyde were detected above baseline levels and their concentrations were well below threshold levels for exposure under a variety of U.S. and international exposure standards (Mitova 2016).

- Standard toxicological assessment:
  In vitro and in vivo studies were conducted to determine whether THS aerosol was significantly less toxic than cigarette smoke.

    - Three in vitro assays were conducted to compare the toxicity of the THS aerosol with cigarette smoke. In the first test (Neutral Red Uptake), the in vitro cytotoxicity of the THS aerosol was reduced by approximately 90%; in the second test (Ames Assay), no bacterial mutagenicity was observed at the tested dose range for THS, whereas reproducible mutagenic responses were observed for cigarette smoke; and in the third test (Mouse Lymphoma Assay), which investigates mammalian mutagenicity, the aerosol from THS was at least eight-fold less mutagenic (Schaller 2016).

- In two inhalation toxicity in vivo studies, laboratory animals exposed to the THS aerosol had reduced exposure to HPHCs, which led to reduced lung inflammation, which in turn led to reduced respiratory pathology findings (Wong 2016, Sewer 2016, Oviedo 2016, Kogel 2016).

- Innovative Systems Toxicology assessment:
  Systems toxicology relies on state-of-the-art high-throughput experimental technologies and advanced computational sciences to determine whether reduced toxicity leads to reduced risk in laboratory models. Systems toxicology enables a detailed assessment of the disease-relevant biological mechanisms affected by exposure to toxicants (Hoeng 2012, Sturla 2014). Several studies were conducted to compare the effects of the THS aerosol with those of cigarette smoke. These include:

  - Four studies were conducted *in vitro* to compare the biological effects of the THS aerosol with those of cigarette smoke on human organotypic tissue cultures of oral (Zanetti 2016), gingival (Zanetti 2017), nasal (Iskandar 2016), and bronchial (Iskandar 2017) epithelia. In all studies, the THS aerosol had a significantly reduced effect on all mechanisms affected by cigarette smoke.

  - A study was conducted in an animal model (Apoe$^{-/-}$ mouse) that develops atherosclerotic plaque and emphysema when exposed to cigarette smoke (Lo Sasso 2016). In this study, mice were exposed to either cigarette smoke or THS aerosol for 8 months. Furthermore, a group of mice was first exposed for two months to cigarette smoke and then randomized to either THS aerosol (switching) or fresh air (cessation). Switching to THS aerosol was shown to reduce the development of both atherosclerosis and emphysema in a manner similar to smoking cessation. A detailed analysis of the molecular mechanisms affected by smoke exposure in the lung showed that switching to THS aerosol reduced the overall biological impact in a way that approached cessation and that long-term exposure to the THS aerosol has only little effect on these mechanisms compared with cigarette smoke exposure (Phillips 2016).

- Clinical studies:
  PMI's application includes three types of clinical studies: pharmacokinetic/pharmacodynamics ("PK/PD") studies; one-week reduced-exposure studies in confinement; and three-month reduced-exposure ambulatory studies. PMI is also conducting a 6+6-month exposure-response study. The clinical trials are conducted following Good Clinical Practices, reviewed by an institutional review board, or an independent ethics committee, and registered on the U.S. government's publicly available website www.clinicaltrials.gov, which is maintained by the National Institutes of Health. The eight completed studies demonstrated that THS (1) delivers nicotine at levels comparable to cigarettes, an important fact to ensure that adult smokers will find the product an acceptable substitute for conventional cigarettes; (2) significantly reduces exposure to 15 harmful toxicants in adult smokers who switched to THS to a degree approaching that of cessation over the study period (Haziza 2016a, Haziza 2016b, Luedicke 2017); and (3) led to favorable changes in clinically relevant risk markers linked to smoking-related diseases and known to reverse upon cessation over the study period.

Part B: "*The product, as it is actually used by consumers, will benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products*."

- Consumer perception and behavior studies:
  PMI conducted nine Perception and Behavior Assessment (PBA) studies in the US with over 10,000 participants to assess risk perception of, comprehension of, and intention to use THS among various adult consumer groups, including adult smokers, young adult smokers, former smokers and never-smokers and to assess in a premarket setting the THS's potential impact on population harm.

    - A series of PBA studies assessed the likelihood of initiation among non-users of tobacco products. Overall, these studies demonstrated that THS is not attractive to adult never-smokers and it is minimally attractive to adult former smokers. Less than 6.4% of adult former smokers and less than 1.1% of never-smokers expressed an intention to use THS.

    - The same PBA studies also showed that the THS communication did not significantly affect the intention to quit among those adult smokers who expressed intention to use THS. Additionally, they understood that THS is not a substitute for cessation.

    - Overall, studies also showed that modified risk messages generated substantial intention to use THS among existing tobacco users, up to 39%.

        - Further, an actual use study showed that after six weeks approximately 15% of the study participants had switched from cigarettes to either exclusive, or predominant, use of THS. The actual use study also showed that there was a low level of misuse of THS, which, in combination with the results from a study assessing usability and comprehension of THS instructions for use, indicates that THS will be used as intended. Finally, the availability of THS did not lead to an increase in study participants' total tobacco product consumption.

- Real-life data from Japan:
  The data from Japan show that a significant proportion of adult THS users switch to the product exclusively (65% in July 2016) with the proportion of exclusive users increasing over time. Early cross-sectional studies on the adult population seem to indicate that the rates of initiation and relapse associated with THS are very low (both around 1%). The real-life observations confirm the PBA study results conducted in the U.S.

- Population health impact modelling:
  PMI has developed, validated and tested a Population Health Impact Model (PHIM) using well-established methods in mathematical modelling and simulation analysis (Weitkunat 2015). Using hypothetical assumptions on the likelihood of THS use, combined with estimated changes in relative disease risk, PMI has conducted multiple simulations to estimate the overall impact of THS on the health of the U.S. population. In all but the most unlikely simulations, the introduction of THS resulted in fewer tobacco-related deaths.

  The "Business Case" for THS assumes that 17% of the smoking population would be using THS within 10 years following its commercial launch (15% THS users and 2% dual users). To understand the range of the potential impact of THS, PMI included two relative exposure conditions for THS:

- Condition 1: THS preserved the effects of cessation by 90% (f-value=0.10),
- Condition 2: THS preserved the effects of cessation by 70% (f-value=0.30).

Under this scenario, at the end of the 20-year simulation the introduction of THS resulted in 70,274 fewer smoking attributable deaths (f-value=0.30), 90,155 (f-value=0.10) and 100,234 in the case where the same consumers were switched to smoking cessation (f-value=0). The degree to which tobacco-related deaths were reduced was primarily influenced by the prevalence of use of THS.

- Postmarket Surveillance:
  PMI will conduct studies to generate qualitative and quantitative data that can help provide evidence of an impact at both individual and population levels once the product is placed on the market.

  - PMI has developed a postmarket assessment program consisting of safety surveillance, cross-sectional surveys and cohort studies to allow for collection of safety data, prevalence of use over time, including initiation and cessation, use patterns, and to evaluate the biomarkers of exposure and effect. PMI will submit the findings from the Postmarket Assessment Program to FDA on an annual basis to ensure that the product continues to be of benefit to the overall health of the U.S. population.

Conclusion

The Tobacco Control Act established a mechanism that can ensure that products, which hold out the hope of reducing risk, are actually tested, reviewed, and made available in the marketplace. FDA has stated that "*The modified risk tobacco product provisions of the FD&C may be valuable tools in the effort to promote public health by reducing the morbidity and mortality associated with tobacco use, particularly if companies take advantage of these provisions by making bold, innovative product changes that substantially reduce, or even eliminate altogether, the toxicity or addictiveness of tobacco products, or both*" (FDA, Modified Risk Tobacco Product Applications: Draft Guidance for Industry, 2012).

Although FDA has yet to review the data, PMI believes that the totality of the evidence generated across a broad array of scientific studies, and presented in PMI's application, shows that THS satisfies the two-part "basis for approval" for a Risk Modification Order of (1) reducing harm and the risk of tobacco-related disease to individual tobacco users and (2) benefiting the health of the population as a whole.

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