

The evidence cited in PMI's MRTP Application indicates that the proposed labeling and warnings for IQOS will mislead consumers, particularly youth, about the product

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An essential condition that FDA is required to consider before permitting the marketing of any modified risk or exposure product (MRTP) is the effect that the MRTP and its marketing will have on consumer understanding and perceptions. According to the FDA Guidance, “All MRTPAs [MRTP applications] must contain evidence to show that the advertising and labeling concerning modified risk products ***enable the public to comprehend the information concerning modified risk and to understand the relative significance of such information in the context of total health*** and in relation to all of the diseases and health-related conditions associated with the use of tobacco products [emphasis added].”¹

For exposure modification orders, “any aspect of the product’s label, labeling, and advertising that would make it a modified risk tobacco product must be limited to an explicit or implicit representation that the product or its smoke does not contain or is free of a substance or contains or presents a reduced level of exposure to a substance.”² Importantly, “***applicants seeking an exposure modification order must demonstrate through testing of actual consumer perception that the proposed labeling and marketing of the product does not mislead consumers into believing that the product is or has been demonstrated to be less harmful, or mislead consumers into believing that the product presents less of a risk of disease than one or more other commercially marketed tobacco products.***”³

To address the effect of marketing on consumer understanding and perception, FDA recommends that applicants submit human studies regarding consumer understanding of the product, including its labeling, marketing and advertising. To inform FDA’s evaluation of the proposed MRTP’s marketing on consumer perception and understanding, the scientific studies submitted by the applicant should include:

¹ FDA, Guidance for Industry, Modified Risk Tobacco Product Applications, March 2012; Section 911(h)(1) of the Family Smoking Prevention and Tobacco Control Act.

² FDA, Guidance for Industry, Modified Risk Tobacco Product Applications, March 2012; Section 911(g)(2)(A)(ii) of the Family Smoking Prevention and Tobacco Control Act.

³ FDA, Guidance for Industry, Modified Risk Tobacco Product Applications, March 2012; Section 911(g)(2)(B)(iii) of the Family Smoking Prevention and Tobacco Control Act.

1. The ability of consumers to understand the modified risk claims and the significance of the information in the context of one's health;
2. Consumers' beliefs about the health risks of using the product relative to other tobacco products, including those within the same class of products;
3. Consumer beliefs about the health risks of using the product relative to cessation aids; and
4. Consumer beliefs about the risks of using the product relative to quitting all tobacco use.⁴

As described in detail below, Philip Morris International (PMI) failed to meet this burden, failed to provide compelling scientific evidence on consumer perception and understanding of the labeling and marketing of its proposed IQOS product, and failed to demonstrate that the labeling and marketing of the product will not mislead consumers. Therefore, FDA should deny PMI's MRTP application for IQOS.

PMI's own data do not support the conclusion that IQOS is less dangerous than conventional cigarettes in terms of effects on these biomarkers of potential harm in American people; any marketing claims of modified risk are fundamentally misleading and should not be permitted.

As a preliminary matter, we have shown in another public comment⁵ that PMI's MRTP application does not support any claim of modified risk in human users. PMI presents data on 24 biomarkers of potential harm in American human users, including measures of inflammation,

⁴ FDA, Guidance for Industry, Modified Risk Tobacco Product Applications, March 2012.

⁵ Glantz S. PMI's Own Data on Biomarkers of Potential Harm in Americans Show that IQOS is Not Detectably Different from Conventional Cigarettes, so FDA Must Deny PMI's Modified Risk Claims. Docket Number: FDA-2017-D-300. November 13, 2017. Tracking number: 1k1-8zrx-juh9. See also the other public comments submitted by UCSF: Springer ML, Nabavizadeh P, Mohammadi L. The evidence PMI presents in its MRTP application for IQOS is misleading and does not support the conclusion that IQOS will not harm endothelial function; independent research done in a more relevant physiological model shows that IQOS harms endothelial function as much as conventional cigarettes. Docket Number: FDA-2017-D-3001. November 20, 2017. Tracking number 1k1-8zxa-mq9v. Chun LF, Moazed F, Matthey MA, Calfee CS, Gotts JE. IQOS emissions create risks of immunosuppression and pulmonary toxicity, so FDA should not issue an order permitting IQOS to be labeled or marketed with reduced risk claims. Docket Number: FDA-2017-D-3001. November 30, 2017. Chun LF, Moazed F, Matthey MA, Calfee CS, Gotts JE. PMI's MRTP application for IQOS does not adequately evaluate potential for hepatotoxicity risk. Docket Number: FDA-2017-D-3001. November 30, 2017. Tracking number 1k1-9039-d91g. St.Helen G, Jacob P III, Nardone N, Benowitz NL. Because PMI application did not report the full range of HPHCs in IQOS aerosol, characterize HPHCs in sidestream emissions, include a non-targeted analysis of chemicals in emissions, or conduct clinical studies to describe exposure to toxicants during dual use with other tobacco products, FDA must deny PMI's application. Docket Number: FDA-2017-D-3001. November 29, 2017. Tracking number is 1k1-902j-m8kv.

oxidative stress, cholesterol and triglycerides, blood pressure, and lung function. These human data are the most important information in the application because they represent direct evidence on how IQOS affects people. Based on details in section 6.1.4.4 of the PMI MRTP application, there is no statistically detectable difference between IQOS and conventional cigarettes for 23 of these 24 biomarkers in Americans in PMI's studies. This is indicated by the fact that 23 of the 95% confidence intervals include zero (i.e., no statistically significant difference).

Moreover, when using the conventional 95% confidence standard for statistical hypothesis testing, one would expect 5% of the tests to yield false positives. Five percent of 24 tests is 1.2 tests, which means that one would expect 1 or 2 false positive results. PMI had one positive result, which is what one would expect by chance.

PMI's entire analysis is based on comparisons with conventional cigarettes, which ignores a wide range of other tobacco products, including e-cigarettes, which are often represented as less dangerous than cigarettes.

PMI's analysis of relative harm is based on comparison of IQOS with conventional cigarettes, and does not compare IQOS to any other tobacco products, including e-cigarettes, which the tobacco industry represents as less dangerous than cigarettes. The Perception and Behavioral Assessment studies did assess how adults perceive risks from IQOS as compared to combustible cigarettes, e-cigarettes, and NRT. However, clinical studies only compared IQOS emissions to combustible cigarettes. It is therefore unclear on what information consumers based their comparative perceptions, and it is likely that those perceptions are incorrect. There are numerous studies showing that people perceive lower harm from all tobacco products, compared to cigarettes; however, what is important is to examine how perceptions of IQOS compare to newer, and arguably more popular, products on the market, such as e-cigarettes.

Since e-cigarettes were first introduced in the U.S. less than a decade ago, there has been a rapid rise in the use of e-cigarettes,⁶ a nicotine product that has been marketed with claims of reduced harm similar to PMI's claims about its IQOS product. E-cigarette use is especially common among adolescents and young adults. On the U.S. market since 2007, past 30-day use of e-cigarettes has surpassed use of conventional cigarettes, with use prevalence of 11.3% among high school students (8.0% for cigarettes).⁷ Among young adults 18-24 years old, 23.5% have

⁶ McMillen RC, Gottlieb MA, Schaefer RM et al., Trends in Electronic Cigarette Use Among U.S. Adults: Use is increasing in both smokers and non-smokers. *Nicotine Tob Res.* 2015 Oct;17(10):1195-202

⁷ Jamal A, Gentzke A, Hu SS, et al. Tobacco Use Among Middle and High School Students — United States, 2011–2016. *MMWR Morb Mortal Weekly Rep* 2017; 66:597–603. DOI: <http://dx.doi.org/10.15585/mmwr.mm6623a1>; Syamlal G, King BA, Mazurek JM. Tobacco Use Among Working Adults — United States, 2014–2016. *MMWR Morb Mortal Weekly Rep* 2017;66:1130–1135. DOI: <http://dx.doi.org/10.15585/mmwr.mm6642a2>; see also Centers for Disease Control and Prevention. "National Youth Tobacco Survey (NYTS)." 2015. Web. 22 Aug. 2016; Centers for Disease Control and Prevention "Youth and Tobacco Use." 2016. Web. 22 Aug. 2016; Barrington-Trimis JL, Urman R, Leventhal AM, et al. E-cigarettes, cigarettes, and the prevalence of adolescent tobacco use. *Pediatrics.* 2016;138(2):10.1542/peds.2015-3983. Epub 2016 Jul 11; Gilreath TD, Leventhal A, Barrington-Trimis JL, et al. Patterns of alternative tobacco product use: Emergence of hookah and E-cigarettes as preferred products amongst

ever used an e-cigarette.⁸ Youth are also most likely to use flavored e-cigarette and other tobacco products.⁹ As such, there is reasonable concern that adolescents will compare IQOS to e-cigarettes when assessing risk reduction, and will be more likely to try IQOS products.

PMI's arguments that modified risk claims will not attract nonsmokers are illogical and inconsistent with the available evidence.

PMI's application states that adult never-smokers in their study reported greater perceptions of risk for IQOS than current or former smokers (section 6.4.4.1-3), and argues that IQOS will not cause or motivate "non-users to be interested in the product because it is still considered a risky product" (section 6.4, p. 70). PMI's reasoning and interpretation of their results is not logical. Many studies have shown that non-tobacco users report greater perceptions of tobacco-related risk, compared to tobacco users.¹⁰ However, you cannot then extend these findings to mean that non-users will never go on to use tobacco. Perceptions can change over time, and across products. Instead, the question is how non-tobacco users perceive IQOS compared to other tobacco products, and whether the marketing and appeal of this new tobacco product will result in lower perceptions of risk of IQOS compared to other tobacco products, which then will result in use.

In addition, PMI ignores the fact that most tobacco use begins before age 18. There is no reason to expect that IQOS would be any different, particularly in light of the fact that e-cigarettes, a similar product, have been more popular with youth than adults.

The question PMI should have asked (and that the FDA should ask) is whether IQOS, with lower perceived risks, encourages never-smokers -- including adolescents and young adults -- who would otherwise not use any tobacco products to be more likely to try the IQOS product.

youth. *Journal of Adolescent Health*. 2016;58(2):181-185; NIDA. Tobacco/nicotine and E-cigs. <https://www.drugabuse.gov/drugs-abuse/tobacconicotine-e-cigs>. Updated 2017. Accessed 09/12, 2017.

⁸QuickStats: Percentage of adults who ever used an e-cigarette and percentage who currently use e-cigarettes, by age group. National Health Interview Survey, United States, 2016. MMWR Morb Mortal Weekly Report, 2017;66:892. DOI: <http://dx.doi.org/10.15585/mmwr.mm6633a6>

⁹Ambrose BK, Day HR, Rostron B, et al. Flavored tobacco product use among us youth aged 12-17 years, 2013-2014. *JAMA*. 2015;314(17):1871-1873; Brown JE, Luo W, Isabelle LM, Pankow JF. Candy flavorings in tobacco. *N Engl J Med*. 2014;370(23):2250-2252; Feirman SP, Lock D, Cohen JE, Holtgrave DR, Li T. Flavored tobacco products in the United States: A systematic review assessing use and attitudes. *Nicotine Tob Res*. 2016;18(5):739-749; Wagoner KG, Cornacchione J, Wiseman KD, Teal R, Moracco KE, Sutfin EL. E-cigarettes, hookah pens and vapes: Adolescent and young adult perceptions of electronic nicotine delivery systems. *Nicotine Tob Res*. 2016.

¹⁰Roditis, M., Delucchi, K., Cash, D., & Halpern-Felsher, B. Adolescents' Perceptions of Health Risks, Social Risks, and Benefits Differ across Tobacco Products. *Journal of Adolescent Health*. 2016 May, 58(5):5558-66.

In making its determination on whether to issue an MRTP order, FDA is required to take into account “the increased or decreased likelihood that persons who do not use tobacco products will start using the tobacco product that is the subject of the application.”¹¹ To help inform its decision, FDA should consider the recent and well-documented experience with e-cigarettes. In particular, exposure to e-cigarette advertisements causes increases in smoking urge among adult former and current smokers,¹² reduces adolescent never-smokers’ perceived risks of regular cigarettes,¹³ and has been shown to be associated with increased chances of use in cross-sectional¹⁴ and longitudinal studies.¹⁵

In addition, the fact that e-cigarettes are perceived as less harmful than regular cigarettes by adolescents and young adult never-smokers¹⁶ is one reason that they are often the first tobacco product adolescents and young adults use, which also predicts future cigarette use.¹⁷ According to PMI’s application, while non-smokers’ perceived risk score for IQOS are higher than current and former smokers in PMI’s studies after seeing the modified risk claims (section 6.4.4.1-3), the scores are significantly lower than the non-smokers’ perception of risks for

¹¹ Section 911(g)(4)(C) of the Family Smoking Prevention and Tobacco Control Act.

¹² Durkin SJ, Bayly M, Wakefield MA. Can E-Cigarette Ads Undermine Former Smokers? An Experimental Study. *Tob Regul Sci*. 2016;2(3):263-277; Maloney EK, Cappella JN. Does Vaping in E-Cigarette Advertisements Affect Tobacco Smoking Urge, Intentions, and Perceptions in Daily, Intermittent, and Former Smokers? *Health Communication*. 2016;31(1):129-138.

¹³ Kim M, Popova L, Halpern-Felsher BL, Ling PM. Effects of E-Cigarette Advertisements on Adolescents’ Perceptions of Cigarettes. *Health communication*. In Press; Petrescu DC, Vasiljevic M, Pepper JK, Ribisl KM, Marteau TM. What Is the Impact of E-Cigarette Adverts on Children’s Perceptions of Tobacco Smoking? An Experimental Study. *Tob Control*. 2016.

¹⁴ Dai, H., & Hao, J. (2016). Exposure to advertisements and susceptibility to electronic cigarette use among youth. *Journal of Adolescent Health*, 59(6), 620-626; Mantey, D. S., Cooper, M. R., Clendennen, S. L., Pasch, K. E., & Perry, C. L. (2016). E-cigarette marketing exposure is associated with e-cigarette use among US youth. *Journal of Adolescent Health*, 58(6), 686-690; Giovenco, D. P., Casseus, M., Duncan, D. T., Coups, E. J., Lewis, M. J., & Delnevo, C. D. (2016). Association between electronic cigarette marketing near schools and e-cigarette use among youth. *Journal of Adolescent Health*, 59(6), 627-634.

¹⁵ Nicksic, N. E., Harrell, M. B., Pérez, A., Pasch, K. E., & Perry, C. L. (2017). Recall of E-cigarette Advertisements and Adolescent E-cigarette Use. *Tobacco Regulatory Science*, 3(2), 210-221.

¹⁶ Roditis, M., Delucchi, K., Cash, D., & Halpern-Felsher, B. Adolescents’ Perceptions of Health Risks, Social Risks, and Benefits Differ across Tobacco Products. *Journal of Adolescent Health*. 2016 May, 58(5):5558-66

¹⁷ Kalkhoran S, Glantz SA. E-Cigarettes and Smoking Cessation in Real-World and Clinical Settings: A Systematic Review and Meta-Analysis. *The Lancet Respiratory Medicine*. 2016;4(2):116-128; Leventhal AM, Strong DR, Kirkpatrick MG, et al. Association of Electronic Cigarette Use with Initiation of Combustible Tobacco Product Smoking in Early Adolescence. *JAMA*. 2015;314(7):700-707; Miech R, Patrick ME, O’Malley PM, Johnston LD. E-Cigarette Use as a Predictor of Cigarette Smoking: Results from a 1-Year Follow-up of a National Sample of 12th Grade Students. *Tob Control*. 2017.

regular cigarettes. *Like e-cigarettes, PMI's results show that non-smokers (which would include adolescents, young adults, and former smokers) are more likely to try IQOS than regular cigarettes.*

A larger concern about PMI's modified risk claim is that IQOS's labeling and marketing can mislead non-smokers and former-smokers into initiating or re-initiating tobacco use. While some marketing materials mention that IQOS is "not for non-smokers" (e.g. Module 4, A4.1.1, "Brochure Reduced Risk Claim (Important Warning)", p.3), this statement is not predominantly displayed and thus can easily be overlooked by consumers or misunderstood.

Thus, exposure to modified risk claims in IQOS marketing may lead to an increase in exposure to harmful and potentially harmful chemicals in e-cigarettes among never- and former-smokers, including adolescent never-smokers who initiate nicotine use with IQOS.

PMI's application failed to analyze how IQOS labeling and marketing would affect former smokers. The evidence cited in PMI's MRTP application (Section 6.3.2.2.4.2.1) states that relapse to smoking is common among former smokers.. For youth, the cut-off level for susceptibility to cigarettes indicate that only those who choose "Definitely not" are classified as not susceptible, but every other answer (maybe not, maybe yes, definitely yes) qualifies an individual as susceptible. If the same criteria are used, around 66% of former smokers would be susceptible to trying IQOS if offered by a friend (study PBA05). These results should address whether the IQOS product will be viewed as a way to evade smokefree policies or might reframe nicotine use as socially normative, both of which are perceptions associated with e-cigarette marketing, particularly among older adults and former cigarette smokers.¹⁸ *PMI's own premarket perception studies to address the appeal of IQOS to former smokers indicate that a large proportion would be interested in trying it, depending on the cut-off level for susceptibility.*

The law is crystal clear: FDA may only issue a MRTP order if "the applicant has demonstrated that such 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 [emphasis added]."¹⁹ However, PMI has failed to demonstrate that its IQOS product will significantly *reduce* harm or benefit the population as a whole, not solely among current adult cigarette smokers. *Indeed, the labeling and marketing of IQOS would likely increase harm, especially among adolescent non-users who initiate with IQOS, and would thus not benefit the health of the population as a whole, especially "persons who do not currently use tobacco products."*

PMI did not submit evidence showing that IQOS as actually used by consumers would expose them to the claimed reduced level of exposure or risk, and did not submit data and

¹⁸ Cataldo JK, Petersen AB, Hunter M, Wang J, Sheon N. E-cigarette marketing and older smokers: road to renormalization. *Am J Health Behav* 2015;39(3):361-71 (PMC PMC4351761)

¹⁹ Section 911(g)(1) of the Family Smoking Prevention and Tobacco Control Act.

information demonstrating that consumers actually would switch completely to IQOS, rather than use IQOS concurrently with other tobacco products.

Section 911(d)(6) requires that MRTP applicants must submit “data and information on how consumers actually use the tobacco product,” and the Guidance recommends that applicants submit data and information specifically addressing “concurrent use of multiple products containing nicotine or tobacco.”

Rather than presenting the needed evidence, PMI’s MRTP application is based on the premise that smokers who completely switch to IQOS would realize health benefits and reduced harm. PMI’s application merely assumes that people who switch to IQOS will not use other tobacco or nicotine products. PMI ignores evidence that adolescent and young adult smokers who use novel tobacco products often use two or more kinds of tobacco products concurrently.²⁰ PMI’s MRTP application also ignores the fact that most smokers who use e-cigarettes do not switch completely from cigarettes to other tobacco products.²¹

The experience with e-cigarettes, which have also been promoted with harm reduction and “smokeless” messages, is directly relevant to adolescents’ likely reaction to IQOS. In addition, both have a modern hi-tech image, another common characteristic that raises concerns that IQOS will attract youth. Many adolescents at low risk of initiating nicotine use with conventional cigarettes initiate with e-cigarettes.²² Adolescents who initiate nicotine use with e-cigarettes are more susceptible to smoking combustible cigarettes.²³ This experience with e-cigarettes raises

²⁰ Jamal A, Gentzke A, Hu SS, Cullen KA, Apelberg BJ, Homa DM, et al. Tobacco use among middle and high school students - United States, 2011-2016. *MMWR Morb Mortal Wkly Rep.* 2017;66(23):597-603.

²¹ Messer K, Vijayaraghavan M, White MM, Shi Y, Chang C, Conway KP, Hartman A, Schroeder MJ, Compton WM, Pierce JP. Cigarette smoking cessation attempts among current US smokers who also use smokeless tobacco. *Addict Behav.* 2015 Dec;51:113-9. doi: 10.1016/j.addbeh.2015.06.045. Epub 2015 Jul 4.

²² Dutra, LM, Glantz, SA. E-cigarettes and national adolescent cigarette use: 2004-2014. *Pediatrics.* 1239(2), 2017; Wills TA, Sargent JD, Knight R, Pagano I, Gibbons FX. E-cigarette use and willingness to smoke: a sample of adolescent non-smokers. *Tob Control.* 2016 Apr;25(e1):e52-9; Barrington-Trimis JL, Urman R, Leventhal AM, et al. E-cigarettes, cigarettes, and the prevalence of adolescent tobacco use. *Pediatrics.* 2016;138(2):10.1542/peds.2015-3983. Epub 2016 Jul 11

²³ Barrington-Trimis JL, Urman R, Leventhal AM, et al. E-cigarettes, cigarettes, and the prevalence of adolescent tobacco use. *Pediatrics.* 2016;138(2):10.1542/peds.2015-3983. Epub 2016 Jul 11; Association Between Initial Use of e-Cigarettes and Subsequent Cigarette Smoking Among Adolescents and Young Adults: A Systematic Review and Meta-analysis. Soneji S, Barrington-Trimis JL, Wills TA, Leventhal AM, Unger JB, Gibson LA, Yang J, Primack BA, Andrews JA, Miech RA, Spindle TR, Dick DM, Eissenberg T, Hornik RC, Dang R, Sargent JD. *JAMA Pediatr.* 2017 Aug 01;171(8):788-797; Barnett TE, Soule EK, Forrest JR, Porter L, Tomar SL. Adolescent electronic cigarette use: Associations with conventional cigarette and hookah smoking. *Am J Prev Med.* 2015;49(2):199-206; Miech RA, O'Malley PM, Johnston LD, Patrick ME. E-cigarettes and the drug use patterns of adolescents. *Nicotine Tob Res.* 2016;18(5):654-659; 16. Leventhal AM, Strong DR, Kirkpatrick MG, et al. Association of

the concern that adolescents and young adults will use both IQOS and other tobacco products concurrently, just as adolescents and young adults are dual and poly-users of e-cigarettes along with other tobacco products.²⁴

Indeed, PMI's application indicates substantial dual use of IQOS and conventional cigarettes as actually used. PMI reports (section 3.5.3 and 6.2.2) that 22.4% of US study participants still were using both regular combustible cigarettes and IQOS after 6 weeks. In other countries, dual use of IQOS and combustible cigarettes ranged from 27% (Germany) to 39% (Switzerland) after 4 weeks (section 3.5.3, Table 5). According to PMI's 2016 full-year report,²⁵ 21-31% of users across multiple countries are dual-users with substantial portion of their tobacco use (>30%) from products other than IQOS, including regular combustible cigarettes. Another 7-15% are "Predominant (70-95% IQOS)" users, meaning they still use regular cigarettes along with IQOS up to 30% of the time. ***The reality of these high levels of dual use contradict the qualifying language included in the proposed IQOS labeling that users must "switch completely" from regular cigarettes to IQOS to get the claimed benefit that underlies all the assessments of the modified risk health effects in other parts of the PMI application.***

PMI does not present compelling evidence that their marketing messages will lead current smokers to switch completely from conventional cigarettes to IQOS.

Tobacco companies have a long history of testing the concept of reduced risk and reduced smoke products similar to IQOS, and consumers in these studies have been uniformly enthusiastic about the concept. However, the actual products have done poorly on the market because they did not deliver on the promises of the concept testing.²⁶

PMI did conduct some studies on consumers' comprehension of the modified risk claims (Section 6.4.4.1). The results showed that out of 2,255 adult participants in the US, 62% to 78% of study participants in different study arms identified the "correct" statement ("the risk of tobacco-related diseases can be reduced by completely switching from CC [conventional cigarettes] to IQOS"; section 6.4.4.1, Table 11). However, it is not clear whether the participants fully understood both of the important concepts included in the statement: "reduced" risks (vs. being risk-free) as well as "completely switching" (vs. dual- or poly-use with regular cigarettes). (In addition, as discussed at the beginning of this comment, PMI's own data do not support the conclusion that IQOS is less dangerous than conventional cigarettes.) ***Thus, PMI did not and***

electronic cigarette use with initiation of combustible tobacco product smoking in early adolescence. *JAMA*. 2015;314(7):700-707; E-cigarette use and willingness to smoke: a sample of adolescent non-smokers. Wills TA, Sargent JD, Knight R, Pagano I, Gibbons FX. *Tob Control*. 2016 Apr;25(e1):e52-9.

²⁴ Barnett TE, Soule EK, Forrest JR, Porter L, Tomar SL. Adolescent electronic cigarette use: *Nicotine Tob Res*. 2016;18(5):654-659; Barrington-Trimis JL, Urman R, Leventhal AM, et al. E-cigarettes, cigarettes, and the prevalence of adolescent tobacco use. *Pediatrics*. 2016;138(2):10.1542/peds.2015-3983. Epub 2016 Jul 11

²⁵ <https://www.pmi.com/investor-relations/overview/event-details/?eventId=5246224>, Slide p. 19

²⁶ Ling PM, Glantz SA. Tobacco industry consumer research on socially acceptable cigarettes. *Tob Control*. 2005 Oct;14(5):e3. Review. PubMed PMID: 16183968; PubMed Central PMCID: PMC1748101.

cannot substantiate their claim that “scientific studies have shown that switching completely from conventional cigarettes to the IQOS system reduces the risks of tobacco-related diseases” and they did not and cannot provide evidence that U.S. adults or adolescents (who are likely users of IQOS) understand the modified risk claims made in their labeling and marketing.

According to PMI’s application (7.3.2; PBA05RRC - 2 csr-app-16_1_1-protocol.PDF), PMI’s research question looked at whether “...completely switching from conventional cigarettes to IQOS: a) can increase the risk of tobacco-related disease, b) can reduce the risk of ..., c) has the same risk of tobacco-related diseases, d) can eliminate the risk of ..., e) don’t know.” (#44, p.89) However, as presented, this question cannot measure whether the participants understood the phrase “completely switching” and therefore fails to demonstrate at least two important factors that FDA deemed critically important to its review of MRTP applications: (1) whether consumers fully “understand the modified risk claims and the significance of the information in the context of ones health,” or (2) whether consumers truly understand “the health risks of using the product.”²⁷ Rather, this question can only test the recognition of the terms “reduced” vs “eliminates,” since all response options included the phrase “completely switch.” According to the results, less than 6% of participants selected the response that IQOS “eliminates” the risks, which PMI interpreted to indicate that participants did understand the “reduced” risks of IQOS compared to regular cigarettes. ***However, given the response options available to study participants, the question whether consumers fully understood “switching completely” remains untested.***

Given that PMI’s research attempted to test understanding of “switching completely” but embedding the concept within the response option for “reduced” risks (“the risk of tobacco-related diseases can be reduced by completely switching...”), we do not have a way to tell whether the participants chose that response because they noticed or understood what was meant by the words “completely switching” from regular cigarettes to IQOS or whether they were interpreting the response differently. Participants were not asked to compare risks of using IQOS vs. using IQOS and regular cigarettes vs. only using cigarettes. The question of whether people truly understand “switching completely” also remains unaddressed in the second quantitative study (Section 6.4.4.2 where PMI tested the effect of a different claim “Switching completely to IQOS presents less risk of harm than continuing to smoke cigarettes” on 2,247 adults’ perceptions of IQOS in the US) and the third quantitative study (Section 6.4.4.3 where PMI tested the effects of reduced exposure claim “Switching completely from conventional cigarettes to the IQOS system significantly reduces your body’s exposure to harmful and potentially harmful chemicals” on 2,272 adults’ perceptions of IQOS in the US). ***The fact that more than 25% of actual users of IQOS are using regular combustible cigarettes may be due to the insufficient communication and comprehension of the need to switch completely.***

To support their reduced risk marketing claim, PMI also conducted focus groups and in-depth interviews with adult participants to assess risk perceptions related to IQOS (THS 6.4 Consumer Understanding and Perceptions). Participants were presented with different types of claims (e.g., reduced exposure versus reduced risk) and varying levels of specificity (e.g., general health claims versus specific health claims). For instance, participants were presented

²⁷ FDA, Guidance for Industry, Modified Risk Tobacco Product Applications, March 2012.

with general claims such as “switching to THS 2.2 can lower several risk factors that could lead to smoking-related diseases,” and specific claims such as “switching to THS 2.2 can lower your cardiovascular risk.”²⁸ *None of the scenarios discussed the potential general or specific risk of dual and/or poly-use among current smokers who are unable to switch completely to IQOS.*

The tested claims inappropriately assumed cardiovascular benefit despite the fact that PMI’s own data presented in the application show no significant differences in biomarkers of potential harm for cardiovascular disease in their human studies.²⁹ Participants’ quotes were generally positive toward the use of IQOS, but it is unclear whether the opinions stemmed from a consensus among participants or whether only a minority of participants expressed those views. It was unclear how much, if any, evidence was provided to support the claims of reduce tobacco-related disease or reduced harm. Thus, claims by PMI that participants “correctly” comprehended the inherent risks related to IQOS are incomplete without understanding the context in which focus group discussions were conducted.

Furthermore, the two qualitative studies only used 10 non-smokers. For example, in the study THS-PBA-02-US, only 6 non-smokers participated in individual interviews. Of these six non-smokers, only two were 21-36 years old (which could be considered as young adult) – one male and one female. The conclusion that never smokers are not interested in these products that the report makes is based on only 6 never smokers, most of whom were beyond the age of tobacco initiation.

In quantitative studies, PMI reported creating a new risk perception instrument that included an 18-item perceived health risk scale, a 7-item perceived addiction risk scale, and a 2-item perceived harm to others scale. PMI reported that THS was on average “8 and 22 points lower than CC on the 0 to 100 perceived health risk scale” (THS 6.4 Consumer Understanding and Perceptions). PMI claims that their development and assessment studies demonstrated that the majority of smoking and non-smoking participants consistently ranked THS as lower risk compared to combustible cigarettes but higher risk compared to e-cigarettes and nicotine replacement therapy. Nonsmokers had a higher risk perception compared to smokers. These findings need to be interpreted in the context of the measurement instrument used in the study.

Questions in the PMI’s “Perceived Risk Instrument” provided conditional scenarios, for example, “What do you think is the risk, if any, to you personally of getting the following (sometime during your lifetime) because you smoke cigarettes...” However, these scenarios were very generic. Compare, for example, to specific scenarios used by Halpern-Felsher et al³⁰... “Imagine that you just began smoking. You smoke about 2 or 3 cigarettes each day. Sometimes you smoke alone, and sometimes you smoke with friends. What are the chances of...?” PMI’s questions also did not specify the amount of use (i.e., how much a person smokes), presence of

²⁸ THS Messages tested in THS-PBA-02-US, Table 3, MRTPA section 6.4, page 14.

²⁹ Glantz S. PMI’s Own Data on Biomarkers of Potential Harm in Americans Show that IQOS is Not Detectably Different from Conventional Cigarettes, so FDA Must Deny PMI’s Modified Risk Claims. Docket Number: FDA-2017-D-300. November 13, 2017.. Tracking is 1k1-8zrx-juh9.

³⁰ Halpern-Felsher, B. L., Biehl, M., Kropp, R. Y., & Rubinstein, M. L. (2004). Perceived risks and benefits of smoking: differences among adolescents with different smoking experiences and intentions. *Preventive Medicine*, 39(3), 559-567. doi:DOI 10.1016/j.ypmed.2004.02.017

dual use (using cigarettes in addition to another tobacco product), and age of quitting for cessation questions. The use of the different measurement instrument makes comparison with other studies difficult.

In their Perceived Risk Instrument, PMI is measuring absolute perceptions of risk for each product (separately for cigarettes and IQOS), rather than asking direct comparative questions (e.g., “Are (IQOS products) less harmful/equally as harmful/more harmful than (cigarettes)?” Past research has found that when risks are measured for products separately, greater proportion of people perceive alternative tobacco products as less harmful.³¹ When comparative risk is measured with a direct question, a greater portion of participants responds that alternative tobacco products are equally as harmful as cigarettes. ***The choice of indirect and direct questions seems to be guided by tobacco companies’ goals rather than measures of validity.***

For example, in its 2011 Citizen’s Petition to the FDA, RJ Reynolds argued that US consumers overestimate risk of smokeless tobacco because the studies they cited reported that a large portion of the public perceived smokeless tobacco as equally harmful to cigarettes. However, most of the studies cited in that petition used direct way (single question) of measuring perceived harm. When the goal of the tobacco company was to show that the public believes alternative tobacco products are as harmful as cigarettes, direct way of measuring relative risk has been used. In the PMI’s MRTP application, the goal seems to be to demonstrate greater difference in perceptions of risk between various products, so they used indirect way of measuring relative risk. While we have argued for the use of indirect measures,³² some research indicates that direct measures might have closer relationship to people’s behavior.³³ ***Thus, both indirect and direct measures should have been, but were not, used to support the conclusions made in the PMI’s study are not the artifact of their carefully selected measurement tool.***

PMI’s claims of reduced exposure and reduced harm from IQOS do not account for how their product is likely to be actually used, and in particular do not account for the tobacco use behaviors that accompany the introduction of a new tobacco or nicotine product into the market, as was the observed concern with e-cigarettes.

Section 911(g) mandates that FDA may issue a MRTP order *only if* the applicant has demonstrated that the proposed product, *as it is actually used by consumers*, will significantly reduce harm to individual tobacco users and benefit the health of the population as a whole. ***Since PMI’s MRTP application for IQOS fails to take into account how IQOS is likely to be***

³¹ Popova, L., & Ling, P. M. (2013). Perceptions of Relative Risk of Snus and Cigarettes Among US Smokers. *American Journal of Public Health*, 103(11), e21-e23; Wackowski OA, Bover Mandersiki MT, Delnevo C. Comparison of Direct and Indirect Measures of E-cigarette Risk Perceptions. *Tob Regul Sci*. 2016; 2(1): 38-43; Persoskie, A., Nguyen, A. B., Kaufman, A. R., & Tworek, C. (2017). Criterion validity of measures of perceived relative harm of e-cigarettes and smokeless tobacco compared to cigarettes. *Addictive Behaviors*, 67, 100-105.

³² Popova, L., & Ling, P. M. (2013). Perceptions of Relative Risk of Snus and Cigarettes Among US Smokers. *American Journal of Public Health*, 103(11), e21-e23.

³³ Persoskie, A., Nguyen, A. B., Kaufman, A. R., & Tworek, C. (2017). Criterion validity of measures of perceived relative harm of e-cigarettes and smokeless tobacco compared to cigarettes. *Addictive Behaviors*, 67, 100-105.

actually used, PMI has failed to make the required showing and FDA must not issue a MRTP marketing order.

Although some current smokers may switch completely to IQOS and be successful at smoking cessation, some users of IQOS will become dual and/or poly-users, as is the case e-cigarettes, and to some degree, smokeless tobacco. Indeed, as discussed above, PMI's own data show substantial levels of dual use in their test populations. If this were to happen, IQOS could cause significant increased population level harm by increasing nicotine dependence and tobacco-related diseases from the use of more than one tobacco product, as we are seeing with dual-use of e-cigarettes and cigarettes.³⁴

E-cigarettes, like IQOS, are marketed as non-combustible alternatives to conventional cigarettes. PMI does not address the evidence that adolescents believe that e-cigarettes are less harmful than cigarettes and all other tobacco products,³⁵ that e-cigarettes are acceptable and socially normative,³⁶ and that these perceptions and attitudes are directly related to initiation and use of e-cigarettes.³⁷ Despite studies showing negative health effects of e-cigarettes, adolescents report believing that e-cigarettes are safer than cigarettes, can help people quit smoking conventional cigarettes, and contain none or just limited amounts of nicotine. Adolescents also consider e-cigarettes to be trendier, more prevalent, and more acceptable than conventional cigarettes.³⁸ Adolescents who have used e-cigarettes have reported the lowest perceptions of

³⁴ Kalkhoran S, Glantz SA. Modeling the Health Effects of Expanding e-Cigarette Sales in the United States and United Kingdom: A Monte Carlo Analysis. *JAMA Intern Med.* 2015 Oct; 175 (10): 1671-80. doi: 10.1001/jamainternmed.2015.4209.

Mejia AB, Ling PM, Glantz SA. Quantifying the effects of promoting smokeless tobacco as a harm reduction strategy in the USA. *Tob Control.* 2010 Aug;19(4):297-305. doi: 10.1136/tc.2009.031427. Epub 2010 Jun 27.

³⁵ Roditis, M., Delucchi, K., Cash, D., & Halpern-Felsher, B. Adolescents' Perceptions of Health Risks, Social Risks, and Benefits Differ across Tobacco Products. *Journal of Adolescent Health.* 2016 May, 58(5):5558-66 ; Roditis, M.L., & Halpern-Felsher, B. Adolescents' perceptions of risks and benefits of conventional cigarettes, e-cigarettes and marijuana: A Qualitative Analysis. *Journal of Adolescent Health.* 2015 Aug; 57(2); 179-85.

³⁶ Gorukanti, A. Delucchi, K., Ling, P.P, Fisher-Travis, R. Halpern-Felsher, B. Adolescents' Attitudes towards E-cigarette Ingredients, Safety, Addictive Properties, Social Norms, and Regulation. *Preventive Medicine.* 2016 Oct 20.

³⁷ Gorukanti, A. Delucchi, K., Ling, P.P, Fisher-Travis, R. Halpern-Felsher, B. Adolescents' Attitudes towards E-cigarette Ingredients, Safety, Addictive Properties, Social Norms, and Regulation. *Preventive Medicine.* 2016 Oct 20; Roditis, M., Delucchi, K., Cash, D., & Halpern-Felsher, B. Adolescents' Perceptions of Health Risks, Social Risks, and Benefits Differ across Tobacco Products. *Journal of Adolescent Health.* 2016 May, 58(5):5558-66 ; Pepper, JK, Emery, SL, Ribisl, KM, Rini, CM, Brewer, NT. How risky is it to use e-cigarettes? Smokers' beliefs about their health risks from using novel and traditional tobacco products. *J Behav Med.* 2015 Apr;38(2):318-26.

³⁸ Anand V, McGinty KL, O'Brien K, Guenther G, Hahn E, Martin CA. 2015. E-cigarette Use and Beliefs Among Urban Public High School Students in North Carolina. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine.* 57(1):46-51; Hammal F, Finegan BA. 2016. Exploring Attitudes of Children 12–17 Years of Age Toward

harm and more positive attitudes regarding e-cigarettes.³⁹ ***Given that there are no current studies on adolescents' perceptions of IQOS, PMI should have addressed (and the FDA should address) the analogous evidence from e-cigarettes to estimate the effects that IQOS will have on adolescents' willingness to make similar assumptions about the risks associated with IQOS, and will be willing to initiate and use IQOS.***

There are other important parallels with the entry of e-cigarettes into the market that can be used to assess the likely effects of IQOS in the marketplace. Studies on risk perceptions of electronic cigarettes have shown that many users of e-cigarettes perceive these products to be less harmful than cigarettes and to be effective as smoking cessation aids.⁴⁰ An analysis of e-cigarettes retail websites showed that 95% of the 59 included websites made explicit claims that e-cigarettes can aid in smoking cessation or improve health.⁴¹ Websites that compared cigarettes with e-cigarettes stated that e-cigarettes were cleaner (95% of the websites), cheaper (93% of the websites), could be used to circumvent indoor clear air policies (71% of websites), and could aid in smoking cessation (64%). Other studies that evaluated the content of websites of e-cigarette manufacturers in China showed similar claims of health-related benefits, reduced secondhand

Electronic Cigarettes. *Journal of Community Health*. 1-7; Trumbo CW, Harper R. Use and perception of electronic cigarettes among college students. 2013. *J Am Coll Health*. 61(3):149-155. Roditis, M.L., & Halpern-Felsher, B. Adolescents' perceptions of risks and benefits of conventional cigarettes, e-cigarettes and marijuana: A Qualitative Analysis. *Journal of Adolescent Health*. 2015 Aug; 57(2); 179-85.

³⁹ Ambrose BK, Rostron BL, Johnson SE, et al. 2014. Perceptions of the relative harm of cigarettes and e-cigarettes among U.S. youth. *Am J Prev Med*. 47(2 Suppl 1):S53-60; Anand V, McGinty KL, O'Brien K, Guenther G, Hahn E, Martin CA. 2015. E-cigarette Use and Beliefs Among Urban Public High School Students in North Carolina. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine*. 57(1):46-51; Kong G, Morean ME, Cavallo DA, Camenga DR, Krishnan-Sarin S. Reasons for Electronic Cigarette Experimentation and Discontinuation Among Adolescents and Young Adults. *Nicotine Tob Res* 2015;17(7):847-54 (PMC PMC4674436); Chaffee BW, Gansky SA, Halpern-Felsher B, Couch ET, Essex G, Walsh MM. Conditional risk assessment of adolescents' electronic cigarette perceptions. *American Journal of Health Behaviors*; 2015 May; 39(3):421-432; Roditis, M.L., & Halpern-Felsher, B. Adolescents' perceptions of risks and benefits of conventional cigarettes, e-cigarettes and marijuana: A Qualitative Analysis. *Journal of Adolescent Health*. 2015 Aug; 57(2); 179-85. Trumbo & Harper, 2013)

⁴⁰ Roditis M, Delucchi K, Cash D, Halpern-Felsher B. Adolescents' perceptions of health risks, social risks, and benefits differ across tobacco products. *Journal of Adolescent Health*. 2016;58(5):558-566; Kong G, Morean ME, Cavallo DA, Camenga DR, Krishnan-Sarin S. Reasons for electronic cigarette experimentation and discontinuation among adolescents and young adults. *Nicotine Tob Res*. 2015;17(7):847-854; El-Toukhy S, Choi K. A risk-continuum categorization of product use among US youth tobacco users. *Nicotine Tob Res*. 2016.

⁴¹ Grana, RA and Ling P. Smoking revolution: a content analysis of electronic cigarette retail websites. *Am J Prev Med*. 2014; 46(4): 395-403; Klein EG, Berman M, Hemmerich N, Carlson C, Htut S, Slater M. Online E-cigarette marketing claims: A systematic content and legal analysis. *Tobacco Regulatory Science*. 2016;2(3):252-262.

smoke exposure, and utility for smoking cessation.⁴² These explicit claims were made in the absence of consistent evidence pointing to benefits in health or smoking cessation. Furthermore, these claims are often communicated to cigarette smokers and non-smokers alike, including adolescents, leading to the belief that e-cigarettes are a less harmful choice for any user (that is, not just in comparison to cigarette use), which in turn resulted in e-cigarette initiation among non-users.⁴³ In particular, adolescents believe that e-cigarettes are less harmful than cigarettes and all other tobacco products⁴⁴ and that e-cigarettes are acceptable and socially normative (with a sizeable proportion (20-28%) agreeing that it is ok to use e-cigarettes indoors and outdoors).⁴⁵ Such perceptions and attitudes are directly related to initiation and use of e-cigarettes.⁴⁶ Despite studies showing negative health effects of e-cigarettes, adolescents report believing that e-cigarettes are safer than cigarettes, can help people quit smoking conventional cigarettes, and contain none or just limited amounts of nicotine. Adolescents also consider e-cigarettes to be trendier, more prevalent, and more acceptable than conventional cigarettes.⁴⁷ The lowest

⁴² Yao T, Jiang N, Grana R et al., A content analysis of electronic cigarette manufacturer websites in China. *Tob Control*. 2016; 25(2):188-94

⁴³ Gorukanti, A. Delucchi, K., Ling, P.P, Fisher-Travis, R. Halpern-Felsher, B. Adolescents' Attitudes towards E-cigarette Ingredients, Safety, Addictive Properties, Social Norms, and Regulation. *Preventive Medicine*. 2016 Oct 20; Roditis, M., Delucchi, K., Cash, D., & Halpern-Felsher, B. Adolescents' Perceptions of Health Risks, Social Risks, and Benefits Differ across Tobacco Products. *Journal of Adolescent Health*. 2016 May, 58(5):5558-66

⁴⁴ Roditis, M., Delucchi, K., Cash, D., & Halpern-Felsher, B. Adolescents' Perceptions of Health Risks, Social Risks, and Benefits Differ across Tobacco Products. *Journal of Adolescent Health*. 2016 May, 58(5):5558-66 ; Roditis, M.L., & Halpern-Felsher, B. Adolescents' perceptions of risks and benefits of conventional cigarettes, e-cigarettes and marijuana: A Qualitative Analysis. *Journal of Adolescent Health*. 2015 Aug; 57(2); 179-85.

⁴⁵ Gorukanti, A. Delucchi, K., Ling, P.P, Fisher-Travis, R. Halpern-Felsher, B. Adolescents' Attitudes towards E-cigarette Ingredients, Safety, Addictive Properties, Social Norms, and Regulation. *Preventive Medicine*. 2016 Oct 20.

⁴⁶ Gorukanti, A. Delucchi, K., Ling, P.P, Fisher-Travis, R. Halpern-Felsher, B. Adolescents' Attitudes towards E-cigarette Ingredients, Safety, Addictive Properties, Social Norms, and Regulation. *Preventive Medicine*. 2016 Oct 20; Roditis, M., Delucchi, K., Cash, D., & Halpern-Felsher, B. Adolescents' Perceptions of Health Risks, Social Risks, and Benefits Differ across Tobacco Products. *Journal of Adolescent Health*. 2016 May, 58(5):5558-66 ; Pepper, JK, Emery, SL, Ribisl, KM, Rini, CM, Brewer, NT. How risky is it to use e-cigarettes? Smokers' beliefs about their health risks from using novel and traditional tobacco products. *J Behav Med*. 2015 Apr;38(2):318-26.

⁴⁷ Anand V, McGinty KL, O'Brien K, Guenther G, Hahn E, Martin CA. 2015. E-cigarette Use and Beliefs Among Urban Public High School Students in North Carolina. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine*. 57(1):46-51; Hammal F, Finegan BA. 2016. Exploring Attitudes of Children 12–17 Years of Age Toward Electronic Cigarettes. *Journal of Community Health*. 1-7; Trumbo CW, Harper R. Use and perception of electronic cigarettes among college students. 2013. *J Am Coll Health*. 61(3):149-155. Roditis, M.L., & Halpern-Felsher, B. Adolescents' perceptions of risks and benefits of conventional cigarettes, e-cigarettes and marijuana: A Qualitative Analysis. *Journal of Adolescent Health*. 2015 Aug; 57(2); 179-85.

perceptions of harm and more positive attitudes regarding e-cigarettes have been reported by adolescents who have used e-cigarettes.⁴⁸

Given the similarities between IQOS and e-cigarettes (both products are electronic and hi-tech, and are marketed with reduced harm claims, as better alternatives to cigarettes, and with claims of no “smoke”), it is reasonable to expect that IQOS, like e-cigarettes, will be popular with youth. This is particularly likely because youth will make similar assumptions about the risks associated with IQOS as they make about the risks of e-cigarettes, and will be willing to initiate and use IQOS.

Thus, a major gap in PMI's application is the absence of any comparisons with e-cigarettes. PMI must show that the proposed marketing of IQOS will not result in perceptions and behaviors that have been concerning for e-cigarettes: namely, that youth and non-smokers are likely to initiate based on faulty perceptions of the product's harms, and are likely to dual-use the product with other forms of tobacco. While PMI asserts in its application that IQOS products will be marketed exclusively to current cigarette smokers, there is no practical way to restrict sales and use among non-smokers.

In Korea, PMI stresses that IQOS is meant to be used only by established smokers as an alternative to conventional cigarettes (see Figure 1). Nevertheless, a postdoctoral fellow, who is part of the UCSF TCORS and who is a never-smoker, easily purchased IQOS at one of the Korean IQOS stores in June 2017. At one store, a clerk asked the researcher's smoking status and refused to let her in the store because she was not a smoker. ***In another store, however, the staff did not ask the researcher's smoking status, and she easily purchased IQOS in that store.***

Moreover, checking for smoking status in the first store relied on self-report. Unlike checking the consumer's age using government-issued photo ID, smoking status is hard to validate. ***While there was a 15-minute “information session” provided by the staff inside the Korean flagship store before purchase, it focused on how to use the device, and none of the warnings for nonsmokers or former smokers, or emphasis on complete switching (vs. dual use), were provided.***⁴⁹

⁴⁸ Ambrose BK, Rostron BL, Johnson SE, et al. 2014. Perceptions of the relative harm of cigarettes and e-cigarettes among U.S. youth. *Am J Prev Med.* 47(2 Suppl 1):S53-60; Anand V, McGinty KL, O'Brien K, Guenther G, Hahn E, Martin CA. 2015. E-cigarette Use and Beliefs Among Urban Public High School Students in North Carolina. *The Journal of adolescent health: official publication of the Society for Adolescent Medicine.* 57(1):46-51; Kong G, Morean ME, Cavallo DA, Camenga DR, Krishnan-Sarin S. Reasons for Electronic Cigarette Experimentation and Discontinuation Among Adolescents and Young Adults. *Nicotine Tob Res* 2015;17(7):847-54 (PMC PMC4674436) ; Chaffee BW, Gansky SA, Halpern-Felsher B, Couch ET, Essex G, Walsh MM. Conditional risk assessment of adolescents' electronic cigarette perceptions. *American Journal of Health Behaviors*; 2015 May; 39(3):421-432; Roditis, M.L., & Halpern-Felsher, B. Adolescents' perceptions of risks and benefits of conventional cigarettes, e-cigarettes and marijuana: A Qualitative Analysis. *Journal of Adolescent Health.* 2015 Aug; 57(2); 179-85. Trumbo & Harper, 2013)

⁴⁹ Kim M. Philip Morris International Introduces New Heat-Not-Burn Product, IQOS, in South Korea. *Tob Control.* In press.

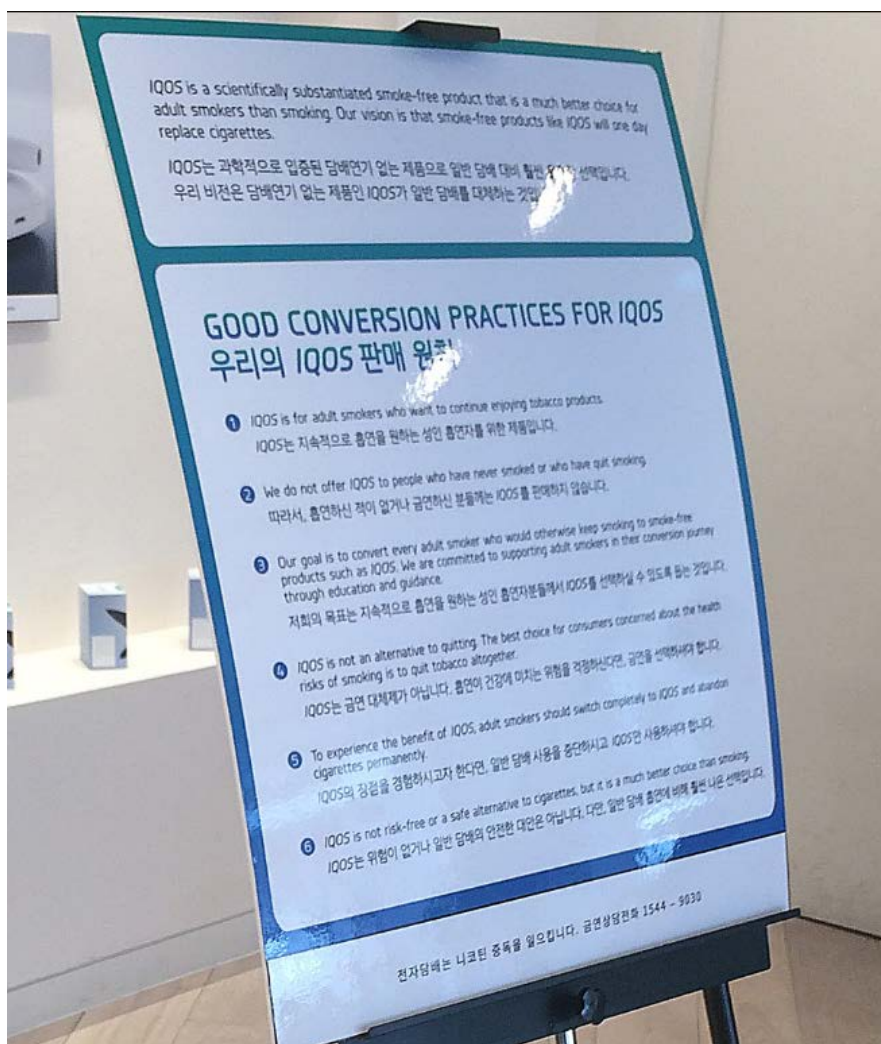


Figure 1. IQOS marketing material in the flagship store in Seoul, Korea. Bullet point #1 asserts that “IQOS is for adult smokers who want to continue enjoying tobacco products. Bullet point #2 asserts that “We [PMI] do not offer IQOS to people who have never smoked or who have quit smoking.” However, although this poster was displayed inside the store, the store staff did not discuss these contents or verify if potential purchasers were current adult smokers or current never smokers. (Picture taken by Minji Kim.)

In addition, limiting purchases by youth and non-smokers online is nearly impossible.⁵⁰ The PMI application does not address this problem at all.

There is sufficient evidence demonstrating that youth under age 18 purchase tobacco products on the Internet. Indeed, the Internet serves as a significant means of acquiring tobacco

⁵⁰ Halpern-Felsher, B. FDA Should Restrict Internet Sales of All Tobacco Products Including E-Cigarettes, Docket No. FDA-2014-N-0189. https://tobacco.ucsf.edu/sites/tobacco.ucsf.edu/files/u9/FDA-Comment-BHF-Submitted%20in%20Response%20to%20FDA%20Deeming%20Rule_Internet%20Sales_FINAL.pdf

for youth, with Internet sales serving as a way to circumvent the age restrictions and face-to-face age verification requirements, given that age verification is virtually non-existent and meaningless.⁵¹ In 2004-2005, youth were 2.6 times more likely to purchase cigarettes over the Internet than were similar students just 4-5 years earlier. The rates went from 1.6% in 2001 to 5.2% in 2005. Moreover, 9% reported that they intended to purchase cigarettes through the Internet.⁵² Furthermore, age restrictions over the Internet are extremely difficult to enforce.⁴⁷

The effects on youth and adolescents are also important, but neither PMI nor any other company should conduct research on youth because this information, collected under the guise of harm reduction or “youth smoking prevention” could easily be used to improve marketing to youth. Rather, as discussed above, the analysis should be done based on current patterns of use of similar products that are already in the market, most notably e-cigarettes.

PMI’s application does not provide compelling evidence that users will understand the need to “switch completely” from cigarettes to obtain the alleged benefit of using IQOS

The following comments should not be interpreted as accepting PMI’s assertion that “switching completely” from conventional cigarettes to IQOS will reduce risk. As discussed at the beginning of this comment, PMI’s own clinical biomarker studies do support the reduced risk claim in humans.

While adults often report a desire to quit smoking as a motivator for e-cigarette use,⁵³ youth most commonly report curiosity as a reason to try e-cigarettes.⁵⁴ It is very plausible that youth would find IQOS to be appealing, similar to how youth attraction to e-cigarettes is enhanced due to curiosity about new technology,⁵⁵ menthol flavor,⁵⁶ and ability to use in places where smoking is prohibited.⁵⁷ It has been consistently reported in multiple, well-controlled

⁵¹ Fix, BV, Zambon M, Higbee C, Cummings KM, Alford T, Hyland A. 2006. Internet cigarette purchasing among 9th grade students in western New York.: 2000-2001. *Preventive Medicine*, 43(3), 191-195, 2006.

⁵² Abrams SM, Hyland A, Cummings KM (2003). Internet cigarette purchasing among ninth-grade students in Western New York. *Preventive Medicine*, 36(6): 731-733.

⁵³ Rutten LJ, Blake KD, Agunwamba AA, Grana RA, Wilson PM, Ebbert JO, Okamoto J, Leischow SJ. Use of e-cigarettes among current smokers: Associations among reasons for use, quit intentions, and current tobacco use. *Nicotine Tob Res* 2015;17(10):1228-34 (PMC PMC4592339)

⁵⁴ Kong G, Morean ME, Cavallo DA, Camenga DR, Krishnan-Sarin S. Reasons for Electronic Cigarette Experimentation and Discontinuation Among Adolescents and Young Adults. *Nicotine Tob Res* 2015;17(7):847-54 (PMC PMC4674436)

⁵⁵ Kong G, Morean ME, Cavallo DA, Camenga DR, Krishnan-Sarin S. Reasons for Electronic Cigarette Experimentation and Discontinuation Among Adolescents and Young Adults. *Nicotine Tob Res* 2015;17(7):847-54 (PMC PMC4674436)

⁵⁶ Krishnan-Sarin S, Green BG, Kong G, Cavallo DA, Jatlow P, Gueorguieva R, Buta E, O'Malley SS. Studying the interactive effects of menthol and nicotine among youth: An examination using e-cigarettes. *Drug Alcohol Depend* 2017;180:193-9 (PMC PMC5659733)

⁵⁷ Bold KW, Kong G, Cavallo DA, Camenga DR, Krishnan-Sarin S. Reasons for Trying E-cigarettes and Risk of Continued Use. *Pediatrics* 2016;138(3) (PMC PMC5005025 conflicts of interest to disclose.)

prospective studies, that youth who experiment with e-cigarettes are at substantially elevated risk of subsequent initiation of cigarette smoking.⁵⁸ ***PMI's MRTP application ignores the fact that based on the public health experience with e-cigarettes, it likely that IQOS would be appealing to these groups, and therefore lead to an increase in tobacco-related harm among youth and current non-smokers.***

Importantly, PMI's proposed claims introduce language ("switching completely," "significantly reduces," and "potentially harmful chemicals") that is unlikely to be familiar to the average tobacco consumer, especially adolescents and youth. It is essential that PMI demonstrate that such claims will be understood by the general public and that consumers' (or potential consumers') interpretations of these claims are aligned with the actual risks of IQOS and HeatSticks. The language used in these claims must be tested thoroughly among the entire population for salience, credibility, readability, and accuracy of consumers' interpretations.

There is reason to believe that potential IQOS consumers will misunderstand the concept of "switching completely." For example, many individuals who engage in smoking do not consider themselves to be smokers,⁵⁹ including large numbers of young adult smokers and >12% of all adult smokers in California.⁶⁰ Smoking cigarettes but not identifying as a smoker is common among non-daily smokers who were formerly daily smokers,⁶¹ opening the likelihood that THS users may consider themselves to have "switched completely" even if they continue to smoke combustible cigarettes.

The law requires PMI to demonstrate that the proposed marketing of IQOS as a MRTP will not result in widespread misperceptions that the IQOS product is a harm-free alternative to combustible cigarettes, and will not lead to substantial product appeal (and subsequent use) among youth, adolescents, and young adults. Until such evidence is available, FDA should reject PMI's MRTP application.

PMI has not provided sufficient evidence that the proposed disclaimers associated with their modified risk or modified exposure claims (i.e., the "PMI IMPORTANT WARNINGS" in Section 6.4.5.1) will assure accurate perceptions of product risk.

PMI proposed the following "important warning" for its modified risk Claim #1:

⁵⁸ Soneji S, Barrington-Trimis JL, Wills TA, Leventhal AM, Unger JB, Gibson LA, Yang J, Primack BA, Andrews JA, Miech RA, Spindle TR, Dick DM, Eissenberg T, Hornik RC, Dang R, Sargent JD. Association between initial use of e-cigarettes and subsequent cigarette smoking among adolescents and young adults: A systematic review and meta-analysis. *JAMA Pediatr* 2017;171(8):788-97

⁵⁹ Leas EC, Zablocki RW, Edland SD, Al-Delaimy WK. Smokers who report smoking but do not consider themselves smokers: a phenomenon in need of further attention. *Tob Control* 2015;24(4):400-3 ; Guillory J, Lisha N, Lee YO, Ling PM. Phantom smoking among young adult bar patrons. *Tob Control* 2017;26(2):153-7 (PMC PMC5067225)

⁶⁰ Leas EC, Zablocki RW, Edland SD, Al-Delaimy WK. Smokers who report smoking but do not consider themselves smokers: a phenomenon in need of further attention. *Tob Control* 2015;24(4):400-3

⁶¹ Leas EC, Zablocki RW, Edland SD, Al-Delaimy WK. Smokers who report smoking but do not consider themselves smokers: a phenomenon in need of further attention. *Tob Control* 2015;24(4):400-3

- Reduced risk does not mean no risk. The best way to reduce your risk of tobacco-related diseases is to completely quit tobacco use.
- *HeatSticks* contain nicotine, which is addictive.
- Using the *iQOS* system can harm your health.

PMI proposed the following “important warning” for its reduced harm Claim #2:

- Less risk of harm does not mean no risk of harm. The best way to reduce your risk of tobacco-related diseases is to completely quit tobacco use.
- *HeatSticks* contain nicotine, which is addictive.

PMI proposed the following “important warning” for its reduced exposure Claim #3:

- It has not been demonstrated that switching to the *iQOS* system reduced the risk of developing tobacco-related diseases compared to smoking cigarettes.
- *HeatSticks* contain nicotine, which is addictive.
- Using the *iQOS* system can harm your health.

PMI compared their own proposed disclaimers to existing Surgeon General warnings; however, new Surgeon General warnings specific to heat-not-burn tobacco have yet to be designed, limiting the relevance of this comparison. Furthermore, disclaimers are often insufficient to correct consumer misperceptions. For example, disclaimers intended to inform consumers that “natural” or “organic” cigarettes are no less harmful than other cigarettes do not deter inaccurate beliefs that natural cigarettes are less harmful.⁶² In fact, government-mandated disclaimers in advertising have been shown to increase consumer confusion and often have effects on consumer perceptions and beliefs opposite of those intended.⁶³

Furthermore, not only should PMI provide evidence that current adult smokers will understand what is meant by the phrase “switching completely,” but the MRTP application should also contain evidence that switching completely from combustible cigarette smoking to the IQOS system will be the predominant use pattern in the US population.

Epidemiologic evidence demonstrates that for other non-cigarette tobacco products, switching completely has not been the most common outcome. Among US adults who use electronic cigarettes, 75% to 82% use e-cigarettes in combination with at least one other form of combustible tobacco,⁶⁴ and only 20% of e-cigarette users are recent quitters of combustible

⁶² Byron MJ, Baig SA, Moracco KE, Brewer NT. Adolescents' and adults' perceptions of 'natural', 'organic' and 'additive-free' cigarettes, and the required disclaimers. *Tob Control* 2016;25(5):517-20 (PMC PMC4887411)

⁶³ Green KC, Armstrong JS. Evidence on the effects of mandatory disclaimers in advertising. *Journal of Public Policy & Marketing* 2012;31(2):293-304

⁶⁴ Kasza KA, Ambrose BK, Conway KP, Borek N, Taylor K, Goniewicz ML, Cummings KM, Sharma E, Pearson JL, Green VR, Kaufman AR, Bansal-Travers M, Travers MJ, Kwan J, Tworek C, Cheng YC, Yang L, Pharris-Ciurej N, van Bemmelen DM, Backinger CL, Compton WM, Hyland AJ. Tobacco-Product Use by Adults and Youths in the United States in 2013 and

cigarettes.⁶⁵ Among adult US males who currently use smokeless tobacco on some days, 45% also smoke cigarettes.⁶⁶ In the data PMI submitted as part of this MRTP application (Executive Summary Figure 35), only 15% of study participants provided with THS (PMI's "Tobacco Heating System") had adopted what PMI labels as a "THS use pattern." More often, participants used both THS and combustible cigarettes.

PMI has not provided a clear definition of what "switching completely" to Tobacco Heat Sticks means. The MRTP application (Executive Summary pages 128 and 147) defines THS use as " $\geq 70\%$ of tobacco products used were HeatSticks" but does not provide the units or measures used to calculate this percentage. It is not known whether this percentage relates to the number of cigarettes and HeatSticks used, total nicotine intake, frequency of use, types of tobacco products used, or some other measure. Lack of knowledge of the actual behavior patterns among PMI study participants impedes adequate interpretation of the research findings. ***Regardless of the specific denominator used, 70% conversion still leaves 30% of consumption as conventional cigarettes, which represents dual use not "switching completely, which would be 100%."***

As is the case for the consumer perception studies, FDA did not post the actual scientific studies upon which PMI's application relies, including the perception and behavior assessment studies, until 5 months after the public comment period began in June 2017. This delay has not allowed sufficient time for researchers and the public to independently verify or analyze the results in detail. FDA should not approve the MRTP application without allowing outside parties sufficient time to review these critical studies.

PMI's packaging, labeling, and brochures do not give specific instructions on how to use the product to get the proposed reduction in risk or exposure, or specific instructions on how to avoid using the product in a way that could reduce or eliminate the potential benefit or increase the risk of using IQOS

PMI's MRTP application for IQOS does not meet the requirements of Section 911(d) because it does not contain the essential "conditions for using the product," i.e., to get the desired reduction in exposure or risk, users must stop using any other tobacco product and use IQOS exclusively. The application mentions that PMI addresses the FDA's guidance on MRTP application to include "specific instructions on how to use and store the product to get the proposed reduction in risk or exposure" (p. 12) in their User Guide (A3.4.1), but the language is limited to using only HeatSticks (e.g. "Never use IQOS holder with a conventional cigarette, or other products/objects", p.7). ***In particular, the IQOS packaging, labeling, instructions for use, users guide, and other advertising materials submitted by PMI do not specifically instruct***

2014. *N Engl J Med* 2017;376(4):342-53 (PMC PMC5317035) ; Weaver SR, Majeed BA, Pechacek TF, Nyman AL, Gregory KR, Eriksen MP. Use of electronic nicotine delivery systems and other tobacco products among USA adults, 2014: results from a national survey. *Int J Public Health* 2016;61(2):177-88 (PMC PMC4819498)

⁶⁵ Weaver SR, Majeed BA, Pechacek TF, Nyman AL, Gregory KR, Eriksen MP. Use of electronic nicotine delivery systems and other tobacco products among USA adults, 2014: results from a national survey. *Int J Public Health* 2016;61(2):177-88 (PMC PMC4819498)

⁶⁶ Tomar SL, Alpert HR, Connolly GN. Patterns of dual use of cigarettes and smokeless tobacco among US males: findings from national surveys. *Tob Control* 2010;19(2):104-9 (PMC PMC2989167)

consumers that they must not use IQOS concurrently with other tobacco products (including conventional cigarettes, e-cigarettes, hookah, or other tobacco products), and do not clearly explain that consumers will not get the stated reduction in risk or exposure if they engage in dual- or poly-use of IQOS products with other tobacco products.

This omission is especially critical for young adult and potential adolescent users, who typically use more than one kind of tobacco product concurrently.^{67,68,69} Importantly, PMI did not submit any studies demonstrating that youth, adolescents, or even adults understand this essential condition for use.

PMI's IQOS labeling and advertising are likely to mislead consumers, especially adolescents and youth

In their MRTP application, PMI includes three proposed label and marketing statements, two focused on claims of reduced risk and one focused on the claim of reduced exposure.

The first proposed label and marketing statement concerning reduced risk states:

Claim #1 (Section 2.7.6 Part B, Table 18):

- The IQOS system heats tobacco but does not burn it.
- This significantly reduces the production of harmful and potentially harmful chemicals.

⁶⁷ McKelvey, K, Ramo, D, Delucchi, K, Rubinstein, M. (Under review) Polydrug use among urban adolescent cigarette smokers. *Addict Behav*; Barnett TE, Soule EK, Forrest JR, Porter L, Tomar SL. Adolescent electronic cigarette use: Associations with conventional cigarette and hookah smoking. *Am J Prev Med*. 2015;49(2):199-206; Miech RA, O'Malley PM, Johnston LD, Patrick ME. E-cigarettes and the drug use patterns of adolescents. *Nicotine Tob Res*. 2016;18(5):654-659.; Haardörfer R, Berg CJ, Lewis M, et al. Poly tobacco, marijuana, and alcohol use patterns in college students: A latent class analysis. *Addict Behav*. 2016;59:58-64; Huh J, Leventhal AM. Progression of poly-tobacco product use patterns in adolescents. *Am J Prev Med*. 2016.

⁶⁸ Barnett TE, Soule EK, Forrest JR, Porter L, Tomar SL. Adolescent electronic cigarette use: *Nicotine Tob Res*. 2016;18(5):654-659; Barrington-Trimis JL, Urman R, Leventhal AM, et al. E-cigarettes, cigarettes, and the prevalence of adolescent tobacco use. *Pediatrics*. 2016;138(2):10.1542/peds.2015-3983. Epub 2016 Jul 11

⁶⁹ Barnett TE, Soule EK, Forrest JR, Porter L, Tomar SL. Adolescent electronic cigarette use: *Nicotine Tob Res*. 2016;18(5):654-659; Barrington-Trimis JL, Urman R, Leventhal AM, et al. E-cigarettes, cigarettes, and the prevalence of adolescent tobacco use. *Pediatrics*. 2016;138(2):10.1542/peds.2015-3983. Epub 2016 Jul 11; Kowitt, SD, Patel, T., Ranney, LM, Huang, LL, Sutfin, EL, Goldstein, AO. Poly-tobacco use among high school students. *Int J Environ Res Public Health*. 2015 Nov; 12(11): 14477–14489. Published online 2015 Nov 13. doi: 10.3390/ijerph121114477. PMCID: PMC4661661; Soneji, S., Sargent, J, Tanski, S Multiple tobacco product use among US adolescents and young adults. *Tobacco control*, 25(2), 2016.

- Scientific studies have shown that switching completely from cigarettes to the IQOS system can reduce the risks of tobacco-related diseases.

The second proposed label and marketing statement concerning reduced risk states:

Claim #2 (Section 2.7.6 Part B, Table 19):

- The IQOS system heats tobacco but does not burn it.
- This significantly reduces the production of harmful and potentially harmful chemicals.
- Switching completely to IQOS presents less risk of harm than continuing to smoke cigarettes.

The third proposed label and marketing statement, concerning reduced exposure states:

Claim #3 (Section 2.7.6 Part B, Table 20):

- The IQOS 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 IQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals.

The law⁷⁰ requires PMI to demonstrate that consumers and potential consumers, including youth and adolescents, will not be misled by labels and advertising. However, there is no evidence that consumers and non-consumers, especially youth, will understand PMI's proposed reduced risk and reduced exposure statements.

The warnings proposed by PMI to be used in their IQOS marketing are particularly problematic when considering youth. The second sentence in the first warning statement ("The best way to reduce your risk of tobacco-related disease is to completely quit tobacco use") should be expanded to add the following phrase at the end: **"including use of nicotine-containing products such as IQOS."** Adolescents who perceive a tobacco product to be "less harmful" compared to cigarettes are more susceptible to use that product.⁷¹ Additionally, when adolescents were polled on their beliefs about risks of smoking "light" cigarettes (a hypothetical "reduced harm" product), it was shown that they felt they would be significantly less likely to get lung cancer, have a heart attack, die from a smoking-related disease, get a bad cough, have trouble breathing, and get wrinkles when smoking light cigarettes, compared with regular cigarettes.⁷²

The second and third warning statements ("HeatSticks contain nicotine, which is addictive," and "Using the IQOS system can harm your health") are virtually meaningless to adolescents. It is well-established that adolescents do not grasp the concepts of harm, including

⁷⁰ Section 911(g)(2)(B)(iii) of the Family Smoking Prevention and Tobacco Control Act.

⁷¹ Ambrose BK, Day HR, Rostron B, et al. Flavored tobacco product use among us youth aged 12-17 years, 2013-2014. JAMA. 2015;314(17):1871-1873

⁷² Kropp, RY, Michels, TM, & Halpern-Felsher, BL. Adolescents' beliefs about the risks involved in smoking light cigarettes. Presented at the American Public Health Association Annual Meeting, San Francisco, CA, November 18, 2003

addiction, or of a substance being addictive. While adolescents have received the message that cigarettes are addictive, they are uncertain regarding the definition of addiction and have not recognized that addiction means experiencing difficulty quitting and continuing to smoke longer than expected.⁷³ Moreover, the same study showing adolescent beliefs about smoking “light” cigarettes⁷⁴ found when participants were asked how long it would take to become addicted to smoking regular or light cigarettes, they thought it would take significantly longer to become addicted to light versus regular cigarettes; that their chances of being able to quit smoking were higher with light versus regular cigarettes; and that they thought it would be significantly easier for them to quit smoking light cigarettes than regular cigarettes.⁷⁵ Furthermore, there is a significant association between regular, experimental, and non-smokers’ perceptions about their personal susceptibility to addiction, with regular smokers showing the greatest optimistic bias about their ability to quit smoking, a measure of addiction.⁷⁶ Finally, evidence shows that smoking initiation is directly related to smoking-related perceptions of risks (“harm”) and benefits. Thus, efforts to reduce adolescent uptake of tobacco products should continue to communicate the particular health risks of smoking and counteract perceptions of benefits associated with smoking.⁷⁷

Because the scientific evidence provided by PMI in support of using these labels does not include youth or adolescents, PMI did not meet its burden of demonstrating that the labels will be understood by and will not mislead the population as a whole. Past research on labels on other tobacco products and advertising suggests that adolescents are likely to misinterpret these messages, believing that the messages being conveyed are simply indicating that IQOS are not harmful.⁷⁸ ***When youth do not adequately understand messages, they make assumptions that the tobacco products are safe, and are more likely to initiate and continue using that product.***⁷⁹

⁷³Roditis, M.L., Lee, J., & Halpern-Felsher, B. Adolescent (Mis)Perceptions about Nicotine Addiction: Results from a Mixed-Methods Study. *Health Education & Behavior*. 2016 April; 43(2):156-64;

⁷⁴ Kropp, RY, Michels, TM, & Halpern-Felsher, BL. Adolescents’ beliefs about the risks involved in smoking light cigarettes. Presented at the American Public Health Association Annual Meeting, San Francisco, CA, November 18, 2003

⁷⁵ Kropp, RY, Michels, TM, & Halpern-Felsher, BL. Adolescents’ beliefs about the risks involved in smoking light cigarettes. Presented at the American Public Health Association Annual Meeting, San Francisco, CA, November 18, 2003

⁷⁶ (Twigg & Byrne, 2015)

⁷⁷ Song, AV, Morrell, HE, Cornell, JL, Ramos, M.E., Biehl, M., Kropp, R.Y., Halpern-Felsher, B.L. Perceptions of Smoking-Related Risks and Benefits as Predictors of Adolescent Smoking Initiation. *American Journal of Public Health*. 2009 Mar; 99(3):487-92. PMID: 19106420.

⁷⁸ Peebles K, Hall MG, Pepper JK, Byron MJ, Noar SM, Brewer NT. [Adolescents' Responses to Pictorial Warnings on Their Parents' Cigarette Packs](#). *J Adolesc Health*. 2016 Dec;59(6):635-641.

⁷⁹ Roditis, M.L., Lee, J., & Halpern-Felsher, B. Adolescent (Mis)Perceptions about Nicotine Addiction: Results from a Mixed-Methods Study. *Health Education & Behavior*. 2016 April; 43(2):156-64.

Furthermore, the proposed "warnings" from PMI are text-only, which will likely limit their effectiveness. Compared with text-only warnings, pictorial warnings on cigarette packs better hold attention, elicit stronger cognitive and emotional reactions and more negative attitudes towards the pack and smoking, and increase intentions to quit smoking.⁸⁰ Additionally, a randomized controlled trial showed that participants who carried cigarette packs labeled with pictorial warnings, compared with those with text-only warnings, were more likely to quit or attempt to quit smoking during the trial, had greater intentions to quit, had more negative emotional reactions and conversations about quitting, and thought more about the harms of smoking.⁸¹ There is strong evidence that compared with text-only warnings, pictorial warnings are more effective in conveying the harms of tobacco product use, are more noticeable, and result in more quit attempts. *Any warnings should include graphic elements to maximize effective communication of the warnings.*

A modified exposure claim is likely to be misunderstood as a modified risk claim, so PMI should not be permitted to market IQOS with a modified exposure claim.

To issue a modified exposure order, section 911(g)(2)(B)(iii) requires the applicant to demonstrate that “testing of actual consumer perception shows that, as the applicant proposes to label and market the product, consumers will not be misled into believing that the product— (I) is or has been demonstrated to be less harmful; or (II) presents or has been demonstrated to present less of a risk of disease than 1 or more other commercially marketed tobacco products.” PMI has failed to meet this burden, so FDA should not grant it a modified exposure order.

The PMI qualitative studies (THS-PBA-02-US and THS-PBA-04-US) explicitly show that consumers perceive reduced exposure claims as reduced risk claims. For example, focus group participants' comments on the “Reduced exposure claim” show consumers’ confusion about reduced exposure claims:

- "It does look nice and it seems like It's going to be less harmful ... (what makes you say It seems like It could be less harmful?) Just the kind of wording: get the flavor and taste satisfaction you expect from a cigarette so it seems like it wants to substitute. It's an innovation of product that maybe is trying to replace the harmful risks that a regular cigarette contains ... " (AS Hale 36-50 Menthol LTN/ SLTN Chicago P2)”
- "It reduces your body's exposure to the chemicals ... that would be my biggest take-away .. it suggests that it is better for you than a traditional cigarette. (Better - In what way?) It's the lesser of two evils; it's a better bad choice ... It reduces harmful chemicals which is likely to reduce your chances of getting a tobacco -related disease." (AS Female 21-34 LTN/ SLTN Phoenix P2)

⁸⁰ Brewer NT, Hall MG, Lee JG, Peebles K, Noar SM, Ribisl KM. [Testing warning messages on smokers' cigarette packages: a standardised protocol](#). Tob Control. 2016 Mar;25(2):153-9.

⁸¹ Peebles K, Hall MG, Pepper JK, Byron MJ, Noar SM, Brewer NT. [Adolescents' Responses to Pictorial Warnings on Their Parents' Cigarette Packs](#). J Adolesc Health. 2016 Dec;59(6):635-641.

In evaluating all claims, the PMI (THS-PBA-02-US Study report) summarized that *all messages (including reduced exposure claims) were perceived by smokers as statements about lower harm. The fact that even the research firm that prepared the report does not distinguish between consumers' perceptions of reduced risk versus their perceptions of reduced exposure provides additional evidence that reduced exposure claims are viewed as reduced risk claims.* For example, this statement related to evaluation of reduced exposure claims appears several times:

“After reading Product Message L, all participants perceive THS 2.2 to be:

- a lower risk of exposure to harmful compounds than conventional cigarettes, but a higher risk than e-cigarettes, NRTs and cessation
- a lower risk of developing tobacco-related diseases than conventional cigarettes, but a higher risk than e-cigarettes, NRTs and cessation.”

In short, the actual reports, transcripts, and data presented by PMI provides FDA with substantial evidence that consumers perceive reduced exposure claims as reduced risk claims, which contradicts what PMI states and directly contradicts the letter and intent of the law.

For a modified risk order, section 911(h)(1) requires any advertising or labeling to “enable the public to comprehend the information concerning modified risk and to understand the relative significance of such information in the context of total health and in relation to all of the diseases and health-related conditions associated with the use of tobacco products.” ***Because PMI failed to demonstrate that the public comprehends these health issues, or that the public can distinguish between “reduced exposure” and “reduced risk” claims, FDA should deny PMI’s MRTP application.***

PMI’s proposed warnings are also problematic, because PMI’s data do not provide conclusive evidence that IQOS provides significant reduction in risks of cardiovascular or other diseases.⁸² Even if the reduced risk claim is dropped, the reduced exposure claim (to harmful and potentially harmful chemicals) can still imply that IQOS is risk-free or poses substantially less risks of tobacco-related diseases. Indirect persuasion using metaphors and implicit claims is widely used in advertisements to make consumers receptive to multiple positive inferences about the promoted product and lead the audience to a conclusion that would be considered misleading if stated directly.⁸³ Comparative claims have shown to mislead consumers to form (erroneous) favorable generalizations on promoted products.⁸⁴ ***Because PMI has not demonstrated that***

⁸² Glantz S. PMI’s Own Data on Biomarkers of Potential Harm in Americans Show that IQOS is Not Detectably Different from Conventional Cigs. Public Comment submitted to FDA (tracking number: 1k1-8zrx-juh9)

⁸³ McQuarrie EF, Phillips BJ. Indirect Persuasion in Advertising: How Consumers Process Metaphors Presented in Pictures and Words. *Journal of Advertising*. 2005;34(2):7-20.

⁸⁴ Andrews JC, Burton S, Netemeyer RG. Are Some Comparative Nutrition Claims Misleading? The Role of Nutrition Knowledge, Ad Claim Type and Disclosure Conditions. *Journal of*

IQOS is associated with lower risks, FDA should not permit PMI to market IQOS with modified exposure claims because such claims are likely to be misunderstood as modified risk claims.

Both the modified risk and modified exposure claims could result in less cigarette cessation.

Based on experience with e-cigarettes, the most common users of e-cigarettes are current cigarette smokers.⁸⁵ Dual use of e-cigarettes with cigarettes is common in the general population, including among low⁸⁶ and very low-income populations.⁸⁷ Nicotine dependence is high among low and very-low-income smokers, and much higher among dual and poly-users.⁸⁸ Higher nicotine dependence is associated with a lower likelihood of successful cessation of combustible cigarettes. Thus, the introduction of IQOS may increase nicotine dependence in a population of smokers that is already highly dependent on nicotine, which may reduce the likelihood of successful cessation of combustible cigarette smoking.

Dual and poly-use of tobacco is associated with decreased successful cessation,⁸⁹ even though dual users may be more likely to make quit attempts.⁹⁰ The claim that switching completely to MRTPs could reduce harm and tobacco-related diseases assumes that people who switch will be more successful at cigarette smoking cessation. However, evidence suggests that cigarette smokers who switch or use other tobacco products for smoking cessation are much less

Advertising. 2000;29(3):29-42.

⁸⁵ McMillen RC, Gottlieb MA, Schaefer RM et al., Trends in Electronic Cigarette Use Among U.S. Adults: Use is increasing in both smokers and non-smokers. Nicotine Tob Res. 2015 Oct;17(10):1195-202

⁸⁶ Kalkoran S, Alavardo N, Vijayaraghavan M et al. Patterns of and reasons for electronic cigarette use in primary care patients. 2017. J Gen Intern Med. [epub ahead of print

⁸⁷ Kish DH, Reitzel LR, Kendzor DE et al., Characterizing Concurrent Tobacco Product use among Homeless Cigarette Smokers. Nicotine Tob Res. 2015; 17(9):1156-60; Baggett TP, Campbell EG, Chang Y, Rigotti NA. Other tobacco product and electronic cigarette use among homeless cigarette smokers. 2016. Addict Behav.60: 124-130; Vijayaraghavan M, Hurst S, Pierce J. A qualitative examination of smoke-free policies and e-cigarettes among sheltered homeless adults. 2017 May;31(3):243-250

⁸⁸ Kish DH, Reitzel LR, Kendzor DE et al., Characterizing Concurrent Tobacco Product use among Homeless Cigarette Smokers. Nicotine Tob Res. 2015; 17(9):1156-60; Baggett TP, Campbell EG, Chang Y, Rigotti NA. Other tobacco product and electronic cigarette use among homeless cigarette smokers. 2016. Addict Behav.60: 124-130

⁸⁹ Zawertailo L, Pavlov D, Ivanova A, Ng G, Baliunas D, Selby P. Concurrent E-cigarette use During Tobacco Dependence Treatment in Primary Care Settings: Association With Smoking Cessation at Three and Six Months. Nicotine Tob Res. 2017 Feb;19(2):183-189 ; Messer K, Vijayaraghavan M, White MM et al., Cigarette smoking cessation attempts among current US smokers who also use smokeless tobacco. 2015. Addict Behav; 51:113-9 ; Popoval L and Ling P. Alternative tobacco product use and smoking cessation: a national study. Am J Public Health. 2013;103(5):923-30 ; Grana R, Popova L, Ling P. A longitudinal analysis of electronic cigarette use and smoking cessation. JAMA Intern Med. 2014;174(5):812-813.

⁹⁰ Messer K, Vijayaraghavan M, White MM et al., Cigarette smoking cessation attempts among current US smokers who also use smokeless tobacco. 2015. Addict Behav; 51:113-9

likely to succeed than people who don't use these products. People who tend to use other tobacco and nicotine products to quit cigarette smoking are more likely to be nicotine dependent and experience difficulty with smoking cessation, evidenced by the increased number of quit attempts, without successful quitting.⁹¹

Because PMI's proposed warnings do not specifically inform consumers that continuing to smoke while using IQOS could reduce the likelihood of quitting smoking, which would result in increased harm, FDA should deny PMI's MRTP application.

Conclusion

PMI did not demonstrate that the proposed marketing of IQOS as a MRTP: 1) will not result in widespread misperceptions that the IQOS product is a harm-free alternative to combustible cigarettes; 2) will not lead to substantial product appeal (and subsequent use) among youth, non-smoking adults, and former smokers; 3) that the proposed marketing claims are consistent with the scientific evidence of actual harm and exposure; 4) that the proposed reduced risk and reduced exposure claims are consistent with how those marketing claims will be interpreted and perceived by potential consumers; and 5) that the proposed labeling will not mislead consumers, especially youth and adolescents, about the health risks of IQOS and the relative risks compared with not using any tobacco product. FDA should deny PMI's MRTP application because it does not include sufficient evidence to address these points.

⁹¹ Messer K, Vijayaraghavan M, White MM et al., Cigarette smoking cessation attempts among current US smokers who also use smokeless tobacco. 2015. Addict Behav; 51:113-9 ; Shi Y, Pierce P, White M et al., E-cigarette use and smoking reduction or cessation in the 201/2011 TUS-PS longitudinal cohort. BMC Pub Health. 2016;16(1):1105.