**Notes on FDA’s** [**Technical Project Lead Review for the IQOS PMTA**](https://www.fda.gov/media/124247/download)

Lauren K. Lempert

Stanton A. Glantz

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| **Page** | **Notes** |
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| 10-14 | **Executive Summary** |
| 11 | Says that since nicotine delivery, addiction potential, and abuse liability are similar to CC, this is “potentially beneficial for smokers trying to switch to IQOS as they are more likely to have satisfactory results and not resume CC smoking.” The FDA does not cite specific evidence to support this speculative statement that PMI is promoting. |
| 11 | Acknowledges that “the nicotine levels do pose an addiction risk for non-tobacco users who initiate use of these products.” |
| 11 | Acknowledges that the applicant’s studies do NOT demonstrate reduction in long-term disease risks. However, said currently available evidence shows CC smokers who “switch completely to IQOS” will have reduced toxic exposures, and this is likely to lead to less risk of tobacco diseases.This ignores the fact that IQOS has HIGHER levels of some toxins than CCs. It just happens that these toxins are not on the HPHC list because they are not in cigs at high levels. (It also provides a hint as to where the MRTP application is headed; permitting PMI’s lower exposure claim, which, as we pointed out in our public comments, will be misinterpreted as lower risk by consumers.) |
| 11 | Says available evidence shows no increase in HPHC exposures for dual users. Also says 5-day studies demonstrate improved biomarkers of exposure (BOE) which indicates reduced HPHC exposures. These statements ignore the fact that PMI’s submission shows that IQOS produces *higher* levels of other toxins that cigarettes. In particular, St. Helen et al (St.Helen G, JacobIII P, Nardone N, et al. IQOS: examination of Philip Morris International’s claim of reduced exposure, Tob Control 2018;27:s30–s36. ) report:PMI reported levels for only 40 of 93 harmful and potentially harmful constituents (HPHCs) on FDA’s HPHC list in IQOS mainstream aerosol. All substances in PMI’s list of 58 constituents (PMI-58) were lower in IQOS emissions compared with mainstream smoke of 3R4F reference cigarettes. However, levels of 56 other constituents, which are not included in the PMI-58 list or FDA’s list of HPHCs, were higher in IQOS emissions; 22 were >200% higher and seven were >1000% higher than in 3R4F reference cigarette smoke. PMI’s studies also show significantly lower systemic exposure to some HPHCs from use of IQOS compared with smoking combustible cigarettes.Conclusion: PMI’s data appear to support PMI’s claim that IQOS reduces exposure to HPHCs. However, *PMI’s data also show significantly higher levels of several substances that are not recognised as HPHCs* by the FDA in IQOS emissions compared with combustible cigarette smoke. The impact of these substances on the overall toxicity or harm of IQOS is not known. [Emphasis added]This information was submitted to FDA as a public comment to the IQOS MRTP application: St.Helen G, Jacob III P, Nardone N, Benowitz N, 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. November 29, 2017. Docket Number: FDA-2017-D-3001, Tracking Number: 1k1-902j-m8kv. Available at: <https://www.regulations.gov/document?D=FDA-2017-D-3001-0129>More important, the impacts of IQOS on clinical measures are more important for assessing impact on health than the biomarkers of exposure, and they did not show any difference in clinical markers of disease risk. See Glantz public comment submitted to MRTP docket discussing the problems with PMI’s study: Glantz SA, PMI’s 6-month study “Evaluation of Biological and Functional Changes in Healthy Smokers After Switching to THS 2.2 for 26 Weeks (ZRHR-ERS-09 US)” submitted in PMI IQOS MRTP June 8, 2018 amendment to FDA-2017-D-3001-0002 does not support claims of reduced risk. December 21, 2018. Docket Number: FDA-2017-D-3001, Tracking Number: 1k2-978f-eqmr. Available at: <https://www.regulations.gov/document?D=FDA-2017-D-3001-0236> |
| 11-12 | More about dual use, and US study. Given that smokers relapse for months after quitting smoking, a 6-week observational period is likely not enough to demonstrate that users who “switch completely” will continue to exclusively use IQOS.More important,PMI’s definition of switching is generally 70% of use from IQOS. That is not switching “completely.” Given the highly nonlinear dose-response relationship for cardiovascular disease this is still enough cigarette consumption to have substantial effects on risk. |
| 12 | IQOS labeling and advertising will be required to include the “nicotine is an addictive chemical” warning, but FDA recommends removal of the “Cigarette smoke contains carbon monoxide” warning, saying it is “misleading” because although IQOS is categorized as “cigarettes,” they do not produce CO above environmental levels and do not increase CO-related health risks. |
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| 12 | FDA concludes that none of the grounds specified in 910(c)(2) for denying the PMTA application apply. Specifically, permitting the marketing of the products is appropriate for the protection of the public health.This is turning the standard on its head.  The FDA is saying something is "appropriate for public health" if it is not worse than cigarettes.  Rather than placing the burden on PMI to demonstrate that IQOS *is* “appropriate for public health” FDA has taken on the burden of demonstrating that IQOS is *not* appropriate for public health, which FDA has improperly defined as “not more dangerous than cigarettes.” The FDA did not consider other products on the market, such as e-cigs, which deliver lower levels of toxins than IQOS. |
| 12 | FDA also concludes that the products do not fail to conform to a tobacco product standard in effect under Section 907. The FDA does not address the issues that we raised about the implicit health claims in the color and design of the packaging. See: Papers: McKelvey K, Popova L, Kim M, et al. Heated tobacco products likely appeal to adolescents and young adults. Tobacco Control 2018;27:s41-s47.Hair EC, Bennett M, Sheen E, et al. Examining perceptions about IQOS heated tobacco product: consumer studies in Japan and Switzerland. Tobacco Control 2018;27:s70-s73.Public comment: Halpern-Felsher B, McKelvey K, Kim M, et al. PMI’s MRTP Application for IQOS Does Not Consider IQOS’s Appeal to Youth or Adolescents, or the Likelihood that Youth and Adolescents will Initiate Tobacco Use with IQOS or Use IQOS with Other Tobacco Products. December 7, 2017. Docket Number: FDA-2017-D-3001, Tracking Number: 1k1-9087-458e. Available at: <https://www.regulations.gov/document?D=FDA-2017-D-3001-0148>  |
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| **14** | 1. **Regulatory History**
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| **14-30** | **B. Product Description: Engineering, Chemistry, Stability, and Manufacturing** |
| 15 | Description of product components. Description of Holder is redacted, but does not mention the computer chip that lets PMI communicate with the device, something that could be used to manipulate the device remotely to increase addictive potential and use. |
| 16 | Heatstick “is not designed or intended to ignite or burn.” The FDA, however, does not address what would happen if someone tries to light it and smoke a Heatstick. |
| 17 | “In the three Heatsticks, glycerol (52.3 mg/Heatstick) is 26% of the total weight of the tobacco in the Heatstick compared to levels of 1-5% typically added to tobacco in CC.[fn 11] In the three Heatstick products, propylene glycol (~2 mg/Heatstick) constitutes 1% of the total tobacco weight. Glycerol degradation produces mainly glycidol and acrolein, while propylene glycol degradation produces acetol and 2-propen-1- ol. Both glycerol and propylene glycol produce formaldehyde, which could increase acrolein generation by IQOS systems with Heatsticks compared to CC; however, the applicant provides data to show this does not occur. (See Section II.C.1.c).” Heatsticks have about 25 times (2500%) more glycerol than CC, and glycerol degradation produces glycidol and acrolein, and 2 mg propylene glycol, whose degradation produces acetol and 2-propen-1-ol. Both of these constituents (glycerol and propylene glycol) produce formaldehyde, which *could* increase acrolein generation compared to CC; however, PMI says this doesn’t occur. Why not? |
| 17 | The total amount of menthol in each Fresh Menthol Heatstick is 13.23 mg, which is 35% higher than the upper limit of menthol reported in the U.S. market for CCs (9.8 mg/cigarette), and 6 times higher (601%) than the lower limit (2.2 mg/cigarette) of menthol in tested CCs. This seems concerning. (The Smooth Menthol Heatsticks contain 6.98 mg menthol/Heatstick.)  |
| 17-18 | The hollow acetate tube and the mouth piece filter on the Heatsticks contain triacetin, which is known to increase the menthol amounts captured in the filter and affect menthol yield, and guar gum, which produces formaldehyde, benzo[a]pyrene, benzene, acetaldehyde, and styrene. How does this protect public health? |
| 18 | Lists carbohydrates, including cellulose in the tobacco, exterior papers, and mouth piece filter, and cellulose acetate in the hollow acetate tube and polylactic acid filter, and says that thermal degradation of carbos produce PAHs, phenols, aldehydes, and ketones. How does this protect public health? |
| 18 | Other constituents of Heatsticks listed, but dismissed as not increasing HPHCs. |
| 18-19 | Higher permeability of the cigarette paper facilitate ventilation with external air, reducing the TNCO yields. “Reducing TNCO yields” translated into a way to get around FTC tests.  |
| 19 | This sounds worrisome, and FDA reviewers relied on “applicant’s assessment” of whether it raises toxic exposure concerns:In PM0000424, epichlorhydrin resin (1.66 mg/Heatstick) is included in the outer paper. Epichlorhydrin has not been identified as a HPHC but has been identified as a potentially toxic hemoglobin adduct formed by inhalation of cigarette smoke. This level is 3-5 times higher compared to levels in non-smokers, but since the paper is not combusted during Heatstick use, FDA chemistry reviewers agree with the applicant’s assessment that the use of epichlorhydrin in Heatstick paper does not raise toxic exposure concerns.The question, however, should not be whether it is “combusted” but rather whether or not it ends up in the IQOS aerosol that the smoker inhales. This could happen without combustion. What is the vapor pressure of this compound? |
| 20  | Describes methodological differences between applicant’s and FDA’s analysis of chemical and physical data. FDA’s Southeast Tobacco Lab used e-cigarette smoking machines, whereas applicant used a 20-port linear smoking machine. So levels of tar, nicotine, ammonia, NNK, and NNN, formaldehyde, benzo[a]pyrene differed. What is the justification for using the two different types of machines and why would the results be different? |
| 21-22 | FDA’s chemistry reviewers considered 8 peer-reviewed studies on chemical analyses and concluded 6 of the 8 reported data similar to applicant, Auer et al was flawed due to methodological issues with the study, and didn’t consider Gideon St.Helen’s paper that showed substantially *higher* levels of some toxins in IQOS than CC. Nevertheless, FDA found that the papers did not raise any concerns. See: St.Helen G, Jacob III P, Nardone N*, et al*., IQOS: examination of Philip Morris International’s claim of reduced exposure*Tobacco Control*2018;**27:**s30-s36. This information was also submitted in a public comment: St.Helen G, Jacob III P, 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. November 29, 2017. Docket Number: FDA-2017-D-3001, Tracking Number: 1k1-902j-m8kv. Available at: <https://www.regulations.gov/document?D=FDA-2017-D-3001-0129> |
| 22-24 | Section on product stability was largely redacted. |
| 25 | Description of holder does not mention the computer chip or PMI’s ability to track and manipulate nicotine delivery customized to individual users to maximize consumption, but has two redacted sections. |
| 25 | Description of Charger mentions changes that were made in an amendment, but what the change is and the reason for the change are redacted. |
| 25-27 | Section on manufacturing, process, and controls is largely redacted. This makes it impossible to consider environmental concerns raised by these processes. |
| 27 | The section on “Quality assurance/sample testing,” contains the first mention that “the Holder and Charger contain microcontrollers and firmware,” but then the relevant information is redacted. It says the Engineering review section discusses the firmware architecture, but the relevant information is redacted. |
| 27-29 | Section on inspection of manufacturing facilities is mostly redacted. This could obscure questions about environmental concerns. (Factories are in Lausanne, Switzerland and Bologna, Italy.) |
| 29-30 | Summary of Engineering, Chemistry, Product stability, and Manufacturing Findings.The engineering review concludes that the PMTAs contain adequate information regarding characterizing the design parameters, describing the manufacturing steps and quality control measures, adequate process controls and quality assurance to ensure that products meet manufacturing specs that minimize variability and product quality, and performance testing to verify the product design. So sounds like they are not necessarily making a judgment about the content of the information, but rather are stating that the information was provided. Also TPL reports that applicant made changes to the Holder and Charger, including a description of the firmware functionality, that are “more likely to lead to a more consistent manufacturing process and improve product reliability,” but says nothing about their impact on public health.The chemistry review concludes that the PMTAs contain sufficient information to characterize the product composition based on adequate information on: the list of components, ingredients and additives; the manufacturing steps and quality control measures; manufacturing specs for REDACTED, nicotine, REDACTED, phenol, carbon monoxide, acrylamide, and menthol; data on chemical endpoints establishing stability through shelf life; product analyses for verifying product formulations; testing data demonstrating that the new products contain significantly lower levels of certain HPHCs including formaldehyde, acrolein, carbon monoxide, NNN, NNK, compared to major types of CCs on U.S. market.The microbiology review concludes that the applicant provided adequate information to demonstrate full product characterization and stability over product shelf-life. |
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| **30-42** | **C. Toxicological Risk Assessment** |
| 30-31 | Regarding HPHCs, FDA acknowledges:The HPHC analysis submitted by the applicant demonstrates that some thermal degradation products that are generated as tobacco burns are also found in Heatstick aerosols, albeit at lower levels. It is possible that other unmeasured constituents may be formed at temperatures below the combustion threshold for tobacco.55 (Ref. 55 is Auer et al, Heat-Not-Burn Tobacco Cigarettes: Smoke by Any Other Name. JAMA Intern Med. 2017 Jul 1;177(7):1050-1052. doi: 10.1001/jamainternmed.2017.1419)See also comment on page 11 showing that IQOS produces *higher* levels of many toxins than CCs. |
| 31 | The applicant submitted the following testing data obtained for PM0000424 – PM0000426 manufactured under commercial manufacturing conditions: * TNCO levels using the ISO regimen
* FDA 18+6: This study measured yields of 18 chemicals on the current FDA HPHC list in the Heatstick aerosols (measured under ISO and modified CI regimens) and six constituents found in Heatstick filler.
* PMI-58 study: This study compared yields of 55 chemicals (measured under the modified CI regimen) on the current FDA HPHC list that are found in Heatstick aerosols and 3R4F smoke. The applicant also reported yields of (b) (4) , nicotine, tar, (b) (4) . For 18 of the aerosol compounds, the applicant compared the levels found in Heatstick aerosols to mean levels in the smoke of 30 commercially available cigarettes. A comparison was also done for six Heatstick filler constituents.

 It is not clear why the names of these tested chemicals are redacted: “The applicant also reported yields of (b)(4)[trade secret redaction], nicotine, tar, (b)(4)[trade secret redaction].”  * Amendment MR0000114 (study 93-FDA-HPHCs) included additional information on yields of all 93 chemicals on the current FDA HPHC list for both Heatstick aerosols and 3R4F smoke. In Heatstick aerosols, levels of 39-40 of the chemicals were too low too to be quantified; for the other 53-54 chemicals that could be quantified, the previously reported levels in the PMI-58 study were verified.

As discussed above (regarding page 11), this analysis ignores many toxins that are present in IQOS aerosol at higher levels than in cigarettes. See:Paper: St.Helen G, Jacob III P, Nardone N*, et al*., IQOS: examination of Philip Morris International’s claim of reduced exposure, *Tobacco Control*2018;**27:**s30-s36 Public Comment: St.Helen G, Jacob III P, 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. November 29, 2017. Docket Number: FDA-2017-D-3001, Tracking Number: 1k1-902j-m8kv. Available at: <https://www.regulations.gov/document?D=FDA-2017-D-3001-0129> * Non-Targeted Differential Screening: This study, submitted in Amendment MR0000097, provides the levels of 80 individual constituents present in the aerosol of one or more of the Heatsticks at higher concentrations than in the mainstream smoke of 3R4F.
* P1 characterization: This study includes chemical constituents present at concentrations higher than 100 ng/Heatstick in the aerosol of MR0000059 under a modified CI smoking regimen.
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| 31 | In the FDA 18+6 study and the Non-Targeted Differential Screening, the applicant compared the quantity of each constituent to data obtained from the Kentucky reference cigarette 3R4F. The comparison was performed both per unit (quantity in Heatstick aerosol compared to quantity in cigarette smoke) and per amount of nicotine.To assess whether allowing IQOS on the market would be appropriate for public health, they should also have done a comparison with an e-cig?  |
| 32 | This is concerning:The non-targeted differential screening of Heatstick aerosols and 3R4F cigarette smoke found 80 chemicals that were either present in higher concentration in Heatstick aerosols than 3R4F smoke or not found in 3R4F smoke: 4 are possibly carcinogenic, 30 are identified by the applicant as Generally Recognized as Safe (GRAS), and 46 additional ingredients (mostly flavoring ingredients). **The applicant indicates the four possible carcinogens** (glycidol, 3-chloro-1,2-propanediol [3-MCPD], 2- furanmethanol, and furfural) **do not pose a toxicological concern** because the levels are below recognized dietary or occupational exposure limits. The applicant provided the following toxicological assessments: * Comparison against occupational exposure limits (OELs)
* Use of OSHA’s Permissible Exposure Limit (PEL) as a standard for some exposures
* Compared the exposure from IQOS aerosol for the four chemicals to maximum dietary intake

FDA states: “**The assessment of these carcinogens is not considered adequate.”** Neither dietary nor occupational exposure limits are relevant.  Diet is a different mode of delivery and occupational limits are typically much higher than ambient limits.  Smoking IQOS is not required as part of anyone's job.The FDA goes on to say this in the next paragraph. Nevertheless, they say these data "do not preclude a conclusion the products are appropriate for protection of public health." This finding reinforces the problem with FDA focusing so narrowly on the HPHC list and not paying attention to things like this. Using OSHA’s PEL is also not appropriate for assessing a consumer product. PELs are of *occupational exposure.* The only people supporting use of OSHA PELs for risk assessment of consumer tobacco products is the tobacco industry. This is a buried implicit policy decision by FDA that run counter to its charge to protect public health.Nevertheless, FDA ultimately concludes: “The data provided by the applicant is not sufficient to support their conclusion that these compounds pose no risk to IQOS users; however, although there is potential for genotoxicity with some of these compounds, the exposure levels appear low and the available data does not preclude a conclusion the products are appropriate for protection of public health.”Again, this provides a glimpse of how FDA might rule on the MRTP application: that while there is a “potential for genotoxicity with some of these compounds, **the exposure levels appear low** and the available data does not preclude a conclusion the products are appropriate for protection of the public health.”The FDA is also shifting the burden of proof away from the industry to provide evidence of lack of harm on to the agency (or the public) to prove harm. This seems inconstant with the whole aim of the law, at least as Mitch Zeller has described it in numerous public appearances. |
| 33 | Data were not provided comparing these levels to 3R4F; however, the applicant indicates there is (b) (4) mg of nicotine in the tobacco filler of an unused Heatstick, but only 1.19-1.29 mg of nicotine is volatilized into the aerosol. The applicant did not provide the nicotine levels for used Heatsticks. The applicant also included measures of tar, water and total particulate matter (TPM). Although TPM is 20- 32% higher in the aerosol of the Heatsticks than in CC, the composition is different. The TPM produced by the IQOS system contains 76% (b) (4) and 10% (b) (4) while the TPM produced by the reference cigarette 3R4F contains 32% water and 5% glycerol. In the three products, the level of tar is 20-36% lower in the aerosol compared to the reference cigarette 3R4F. Why are there (b)(4) trade secret redactions for quantity of nicotine and other ingredients? |
| 33-34 | Compares HPHC yields of only 18 HPHCs in Heatstick aerosol and CCs. As Gideon St.Helen’s paper pointed out, they did not look at all 93 HPHCs?See: St.Helen G, Jacob III P, Nardone N*, et al*., IQOS: examination of Philip Morris International’s claim of reduced exposure*Tobacco Control*2018;**27:**s30-s36. |
| 36 | Regarding PMI’s Mouse Lymphoma Assay to determine clastogenicity and mutagenicity which concluded, among other things that the lowest observed genotoxic effect levels (LOGELs) of the 3R4F GVP (gas vapor phase) were 8-24 times lower than the IQOS GVP, and that this difference in LOGEL is an index of mutagenic potency, FDA notes: “However, guidance from major public health resources (e.g., OECD, ICH, Health Canada, EPA) does not support this method of relative comparisons of mutagenic/genotoxic potency between tobacco products (or other chemicals).  |
| 37 | In its Summary of In Vitro Studies, FDA concludes:Overall, the evidence submitted indicates that although both Heatstick aerosols and 3R4F smoke produce cytotoxic changes in vitro, **3R4F produces cytotoxicity at much lower concentrations than Heatstick aerosols**. Similarly**, both Heatstick aerosols and 3R4F are mutagenic, though 3R4F appears to produce genotoxic effects at a much lower level than Heatstick aerosols.** As noted above, the level of substance required to produce these effects may not be an accurate indicator of mutagenic potency. Consequently, it is difficult to determine from these in vitro evaluations whether long-term use of Heatsticks will have the same carcinogenic potential as CC smoke. The FDA determination that IQOS protects the public health is inconsistent with the FDA’s conclusion that 3R4F cigarettes produce **lower** cytotoxicity and genotoxic effects than IQOS Heatsticks.The FDA dismisses this finding on the grounds that “As noted above, the level of substance required to produce these effects may not be an accurate indicator of mutagenic potency. Consequently, it is difficult to determine from these in vitro evaluations whether long-term use of Heatsticks will have the same carcinogenic potential as CC smoke.” This is another example of the FDA taking on the burden of proving that IQOS are *not* appropriate for the public health, rather than requiring PMI to prove that it *is* appropriate. |
| 37 | In in vivo studies, “The applicant reported urinary levels of BOE to the harmful and potentially harmful constituents NNK (total NNAL), acrolein (HPMA, 3-hydroxypropylmercapturic acid), benzene (SPMA, S-phenylmercapturic acid), and acrylonitrile (CEMA, 2-cyanoethylmercapturic acid) for all groups.” …Overall, the incidence of basal cell hyperplasia (nose and larynx) and squamous cell hyperplasia (nose and larynx) were similar in rats exposed to either Heatstick aerosols or 3R4F. In other words, on this dimension, IQOS are as bad as cigarettes.  |
| 38 | Regarding 18-month carcinogenicity study with A/J mice, FDA notes: “The final report for this study was received September 4, 2018. The applicant concludes the study demonstrated no increase in lung cancer risk due to THS 2.2 aerosol exposure compared to sham group. Per the applicant, toxicity is limited to adaptive responses in the upper respiratory tract organs and stress- related responses to exposure, both of which were of lower severity compared to the mice exposed to 3R4F smoke.” They don't address the evidence that PMI submitted showing that hepatotoxicity of IQOS may be higher than a CC that Chun, Moazed, Matthay, Calfee, and Gotts identified in their paper and public comment.Paper: Chun L, Moazed F, Matthay M, et al., Possible hepatotoxicity of IQOSTobacco Control 2018;27:s39-s40.Public Comment: Chun L, Moazed F, Matthay M, et al., PMI’s MRTP application for IQOS does not adequately evaluate potential for hepatotoxicity risk, November 30, 2017. Docket Number: FDA-2017-D-3001, Tracking Number: 1k1-9039-d91g. Available at: <https://www.regulations.gov/document?D=FDA-2017-D-3001-0133> |
| 39 | In summary: Similar to the in vitro studies**, it is difficult to determine the carcinogenic potential of long-term exposure to Heatstick aerosols from these evaluations. The data suggest there is potential for carcinogenic effects from Heatstick aerosols, but at much higher exposure levels than required for CC smoke.** The 18-month carcinogenicity study results reported by the applicant showed no increase in risk due to the Heatstick aerosol exposure compared to CC smoke and the changes noted were similar to the sham control group. How this correlates with clinical changes in humans is unknown. It seems the application is inconclusive regarding long-term exposure to Heatsicks, but I assume PMI’s goal is for users to smoke IQOS long-term, not just for 90 days. (Indeed, if they only used IQOS for 90 days, or even 6 weeks, PMI cannot claim that smokers “switched completely” to IQOS.) Also, FDA acknowledges that these rodent studies may not correlate with clinical changes in humans. Importantly, this once again suggests that the “reduced exposure” issue may be a key to FDA’s thinking on the MRTP application. |
| 39-40 | Systems Toxicology Studies |
| 39 | Human organotypic tissues studies: “Both 3R4F and Regular Heatstick aerosols produce toxicity (e.g., oxidative stress, DNA damage, increased proinflammatory mediators) in human gingival, bronchial, buccal, nasal, and small airway tissues, as well as epithelial tissues from human coronary arteries.” FDA said the toxic effects produced by 3R4F smoke were generally more severe than by Heatsticks. However, FDA noted problems with the experimental approach used, including that they have not been independently validated, limiting the usefulness of the data submitted.  |
| 39-40 | ApoE Mouse Switching study, intending to model continued cigarette smoking vs switching to Heatsticks vs smoking cessation. FDA notes limitations to the study and results. Importantly, FDA notes that “dual exposure to cigarette smoke and Heatstick aerosol was not evaluated.” |
| 40-41 | Nonclinical evaluation of CO from Heatstick aerosol. Although reconstituted tobacco can produce high levels of CO and nitrogen oxides during combustion, and despite Heatsticks containing only reconstituted tobacco, FDA said applicant showed that Heatsticks produce much lower CO compared to regular CC. FDA then redacted some of what applicant considered to arrive at this conclusion. |
| 41-42 | Summary of toxicological findings:* There are HPHC reductions (although did not look at all 93 HPHCs)
* Heatsticks contain 4 probable or possible carcinogenic chemicals unique to IQOS or present in higher levels that 3R4F smoke, and contain 15 other possibly genotoxic chemicals and 20 more GRAS compounds with potential health effects. Nevertheless, FDA concludes that “when balanced angst the significant decreases in the number of HPHCs and HPHC yields, however, these chemicals, which are present at very low levels, do not raise significant concerns from a public health perspective.”
* TPM from Heatsticks did not show mutagenicity in Ames assay
* NRU assay indicate cytotoxicity for Heatstick TPM and BVP are reduced
* In vitro MLA shows biologically relevant mutagenic response in mammalian cells from Heatstick aerosols. Says “CTP agrees with the public health groups that the level of a substance required to produce a genotoxic effect may not be an accurate indicator of mutagenic potency.” (Not sure what bottom line is here.)
* Data submitted by applicant on pathophysiological changes and adverse effects in organotypic studies considered not helpful because of exploratory methods used that have not been independently validated.
* 90-day inhalation study in rates showed changes less severe than due to 3R4F smoke.
* 8-month mouse switching/cessation study suggested switching to IQOS after a short period of cigarette smoke exposure led to histopathological changes similar to smoking cessation. However, FDA noted study design limitations due not allow reliance on this data.
* 18-month carcinogenicity study showed incidence of neoplastic lesions appeared higher in some groups exposed to either Heatsticks or reference cigarettes as compared to control group. However, other evidence showed repeated exposure to Heatsticks produced fewer histopathological changes than repeated exposure to reference cigarette smoke. Applicant concludes this long-term study showed no increase in lung cancer risk due to IQOS exposure compared to controls.

After considering all the toxicological data presented, the TPL (technical project lead) concluded that the reductions in HPH exposures and the reduced histopathological changes with reduced potential for atherosclerotic effects indicate “the ***potential* for a *relative* benefit compared to CC for smokers who *switch completely* to IQOS**.” Note the qualifying language – “potential” for benefit, not a demonstrated benefit, and that benefit is a “relative” benefit compared to conventional cigarettes (not to e-cigarettes, which should be the comparator product), and only if smokers “switch completely” to IQOS, which PMI’s own data shows is not the predominant use pattern.Also, the TPL concluded that although “some of the chemicals are genotoxic or cytotoxic, these chemicals are present in very low levels and potential effects are outweighed by the substantial decrease in the number and levels of HPHCs found in CC.”The overall conclusion relies significantly on HPHC levels, despite the fact that PMI did not look at all HPHCs, and there were increases in several HPHCs.In addition, the TPL’s conclusion is based almost entirely on cancer with scant attention to CVD. See Matt Springer’s paper and public comment indicating that IQOS is as bad as a cigarette in terms of effects on vascular function, a major factor in CVD.Paper: Nabavizadeh P, Liu J, Havel CM, et al.,Vascular endothelial function is impaired by aerosol from a single IQOS HeatStick to the same extent as by cigarette smokeTobacco Control 2018;27:s13-s19.Public Comment: 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, November 20, 2017. Docket Number: FDA-2017-D-3001, Tracking Number: 1k1-8zxa-mq9v. Available at: <https://www.regulations.gov/document?D=FDA-2017-D-3001-0118> |
| **42-50** | **D. Behavioral and Clinical Pharmacological Assessment** |
| 42-45 | Regarding pharmacokinetics, exposure/response and clinical pharmacology, FDA reviewed PMI’s pharmacokinectic/pharmacodynamic (PK/PD) studies, intrinsic and extrinsic factors affecting nicotine pharmacokinetics, and nicotine equivalents (NEQ) in urine, and concluded overall that the population PK model accounts for the variability in nicotine k among all clinical studies with consideration of the influence of the statistically significant intrinsic (body weight, CYP2A6 activity, sex, and race) and extrinsic (nicotine ISO yield, presence of menthol factors. Based on this model, nicotine PK in smokers who switched to IQOS is similar to those who continued to smoke CC. |
| 45-49 | Regarding behavioral pharmacology, including use behavior and topography (with a chunk redacted on puff typography), product use/consumption, product acceptability (dual use higher in US than Japan, with only 7.5% of cigarette smokers reporting using IQOS >95% of the time at the end of the Actual Use study), and abuse liability (evaluated by self-report questionnaires), FDA concluded (noting limitations for self-reported data): systemic nicotine exposure was similar after single and multiple uses of IQOS and CC (both regular and menthol); nicotine exposures appear sufficient to provide user satisfaction, which can facilitate *partial* or complete switching to IQOS; IQOS use rates were similar to CC use rates; self-report questionnaires found that IQOS produces reinforcing effects reaching or close to levels of CC reinforcement; likeability scores for IQOS increased over the 90-day period for those who used it more consistently, which may indicate the need for an adjustment or transition phase from CC (i.e, *dual use*). Further, FDA concluded that the data indicate that IQOS has addictive potential and abuse liability similar to CC. They said this is important because it shows that IQOS can provide an adequate nicotine source for dependent populations, including current CC users; however, “*there is also a risk tobacco-naïve new IQOS users will develop nicotine addiction*.” |
| 49 | “In the Actual Use study, participants were asked at the end of the observational period (Week 6) about their likelihood to purchase the IQOS system “if the IQOS device were available for $79.99 and a pack of Marlboro HeatSticks were available at a price comparable to a pack of Marlboro cigarettes.” In the overall sample (N=987), nearly 20% of participants reported that they “probably or definitely” would buy IQOS. Findings were similar based on menthol/non-menthol preference, across age groups, and across baseline smoking rates. In a subsample of participants who used THS 2.2 > 70% of the time (Week 6, N=138), nearly 50% reported they “probably or definitely” would buy IQOS. Although descriptive data were provided, this was not listed as an outcome measure. It is unclear if participants assumed that they had already owned the IQOS system and were being asked about buying Heatsticks only, or if they assumed the question was referring to purchasing both the IQOS system and Heatsticks.”Using IQOS 70% of the time is not “switching;” it is dual use. |
| 49-50 | Summary of behavioral and clinical pharmacology findings: The behavioral and clinical pharmacology reviewer (BCP) concluded that the similar systemic exposure to nicotine as well as similar use rates, reinforcement, and withdrawal/craving reduction profiles between IQOS and CC suggest a similar abuse liability, and therefore “***IQOS use may sustain addiction to a similar level as CC in current smokers and have a similar risk of nicotine addiction as CC in nonsmokers.”***TPL reviewer agreed with BCP reviewer’s conclusions that IQOS provides nicotine at a high enough level to satisfy the withdrawal and craving symptoms of current smokers. Also said that the ***“nicotine levels do pose an addiction risk for non-tobacco users who initiate use of these products; however the risk is no higher than for other, currently available, tobacco products.”***FDA’s reviewers found a risk of nicotine addiction in nonsmokers who initiate with IQOS. However, they apparently authorized IQOS because this risk “is no higher than for other, currently available tobacco products.” **This does not seem to be a proper application of the public health standard required for a new tobacco product order.** TCA section 910(c)(2) provides that FDA “shall deny an application if there is a lack of a showing that permitting such tobacco product to be marketed would be appropriate for the protection of the public health,” and the basis of that finding is the increased or decreased likelihood that existing users will quit, and that non-users will start using such products. I don’t see how this standard can be interpreted as whether the risk of addiction “is no higher than for other, currently available tobacco products.” But in this document, FDA seems to be saying that the standard is if a new product is no worse than, but just as bad as, cigarettes, they can and should be authorized. That would allow thousands of new cigarette brands to be introduced into the market. That surely was not the intention of the TCA. |
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| **50-65** | **E. Individual Health Impact** |
| 50-56 | Biomarkers of Exposure (BOE). This report reviewed BOEs for carbon monoxide, 1,3-Butadiene, acrolein, benzene, NNK, CYP1A2 activity, and urine mutagenicity. The selected BOEs correspond with 14 HPHCs identified by FDA as being found in cigarette smoke or filler. Additionally, 1-hydroxypyrene was considered a proxy for PAHs, and HEMA and the aromatic amine o-Toluidine were also measured. FDA said exposures to acetaldehyde, formaldehyde, isoprene and ammonia were not assesses because there are not suitable biomarkers for these exposures. 16 HPHCs plus nicotine (total of 17) were evaluated in clinical studies. |
| 51 | Table 3 – selected HPHCs, chemical class, measured BOE, and toxicity class (carcinogenic, cardiovascular, respiratory, reproductive.)  |
| 55-56 | Summary. The behavioral and clinical pharmacology review (BCP) concluded that the reductions in systemic exposures to 15 BOE seen after ***switching from CC smoking to IQOS “may lead to reduced likelihood of smoking-related diseases.”*** The technical project lead (TPL) reviewer agreed with BCP’s conclusion. TPL noted that although the applicant’s data show reductions in BOE during short-term exposures, “*these measures were not intended to evaluate long-term disease risk.”*  Noted limitations to these trials include: (1) small sample sizes limit extrapolation of results to the entire US population (sub-groups such as ***youth***, low socioeconomic status, minorities); the studies were not designed as nationally representative of the US smoking population (participants were moderate smokers; therefore, data may not generalize to light or non-daily smokers; (2) IQOS, but not own-brand cigarettes, were provided free of charge for participants in the studies, which may affect product use rates; (3) **dual use was not considered**. “***Dual use was particularly common in the Actual Use study and may account for a substantial proportion of IQOS users in a real-world setting. Whether this user population will achieve an exposure reduction when compared to exclusive CC use, and to what magnitude, is unclear;”*** (4) study did not compare to never-users. TPL said “a comparison to never-users would have been helpful to determine to what extent IQOS users (i.e., switchers) are still exposed to HPHCs compared with never users;” (5) **no biomarker studies of secondhand exposure to IQOS** were conducted. “The type of study could have helped to better understand potential risks to non-users. Also, **no comparisons between IQOS and other tobacco products such as e-cigarettes**. “Given that IQOS and e-cigarettes may both be considered by consumers to be a substitute for cigarettes, a comparison of the differences in exposure would be useful.” (TPL said the huge increase in popularity of e-cigs in the US occurred during or after the time the clinical trials were conducted.) Overall, BOE reductions were statistically significant over 5 days and the decreases persisted up to 3 months. Bottom line: ***For those who switch completely from CC to IQOS, reduced BOE exposures, which indicate reduced HPH exposures, “are likely to result in reduced risk of tobacco-related disease although that reduced risk has not been demonstrated in the studies submitted by the applicant.”***The devil is in the listing of limitations of these studies. FDA seems to be “covering its ass” by listing the limitations (much as you would in an academic paper), but it is those very limitations that could/would/should lead people concerned about public health to reach opposite conclusions. In particular, youth were not considered, dual use was not considered, risks to non-users (from second-hand smoke exposure) was not considered, and no comparison was made to e-cigarettes, which is possibly a less harmful tobacco product that is more similar to and a more likely competitor to IQOS. The rationalization that e-cigs just got popular “during the time the clinical trials were conducted” is not convincing; many new studies and amendments to the application were made based on FDA request; FDA should have demanded that studies be conducted comparing IQOS to e-cigs. This statement also tips FDA’s hand on the MRTP application, which will grant claims based on reduced exposure, but not reduced risk. |
| 56-59 | Biomarkers of potential harm (BOPH). Studies included measurements of several BOPH as secondary or exploratory study endpoints to determine if IQOS use resulted in biological changes that may indicate a change in long-term disease risk. Looked at (only) 3 major smoking-associated diseases: CVD, COPD, and lung cancer. The studies assess inflammation, oxidative stress, CV risks, lung function, and genotoxicity and mutagenicity. The FDA ignores Stanton Glantz’ critique of this analysis which shows that these changes are not significant. Paper: Glantz SA, PMI’s own in vivo clinical data on biomarkers of potential harm in Americans show that IQOS is not detectably different from conventional cigarettesTobacco Control 2018;27:s9-s12.Public Comment: Glantz, SA. 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, November 13, 2017, Docket Number: FDA-2017-D-3001, Tracking Number: 1k1-8zrx-juh9. Available at: <https://www.regulations.gov/document?D=FDA-2017-D-3001-0108> |
| 58-59 | Summary of BOPH. The medical, epidemiology, and BCP reviews concluded that: (1) minor improvements in some BOPHs in IQOS relative to CC may not be clinically significant and it is unclear how predictive the chosen BOPs are for long-term tobacco-related disease risk; and (2) while no deaths, CV disease, COPD, or lung cancer were reported during the clinical studies, these diseases have a long latency and are unlikely to be observed during studies of this type. (**LKL reaction** – i.e., useless studies, deliberately chosen because they would reveal nothing.) Epi review noted that BOPH don’t necessarily replace clinical endpoints, and in general there are continued questions about the credibility of BOPH as surrogate endpoints. Statistical reviews concluded that the 2 90-day studies were not designed to ascertain any effect associated with the risk endpoints. “It is not clear from a statistical perspective whether the data generated from the studies are clinically meaningful.” The TPL review agreed with the other reviews, and found that ***“compared with the significant reductions in BOE, the changes in BOPH were less pronounced.”*** Further, ***“Overall, the studies conducted by the applicant have not demonstrated evidence of reduction in long-term disease risks.”*** However, “reduction of inflammation and oxidative stress may eventually lead to reduced disease risks.” “The epidemiology review notes that while the BOPH can be informative with respect to key mechanisms of smoking-related diseases, they are not necessarily replacements of clinical endpoints. In general, there are continued questions about the credibility of BOPH as surrogate endpoints. The statistical reviewers evaluated the two 90-day studies and concluded that they were not designed to ascertain any effect associated with the “risk endpoints.” The BOPH were secondary endpoints and were not the basis for sample size/power calculations; it is not clear from a statistical perspective whether the data generated from the studies are clinically meaningful. As TPL, I agree with the BCP, medical, epidemiology, and statistical reviews. Compared with the significant reductions in BOE, the changes in BOPH were less pronounced. One explanation is that none of the BOPH are specific to tobacco use. Changes in BOPH may be attributed to other factors (e.g., weight, diet, exercise). Also, biologic responses related to exposure to tobacco smoke and reversal of these harmful effects may take more time to manifest than the duration of the ambulatory periods of the current studies; many of the effects, e.g., effects of CC, may not be reversible. These factors limit the interpretation of results related to the effects of long-term exposures. **Comment:** The more direct interpretation is that IQOS is not different from cigarettes.Overall, the studies conducted by the applicant have not demonstrated evidence of reduction in long-term disease risks. BOPH may be informative, however, for understanding potential effects on biological processes such as inflammation and oxidative stress. Long-term tobacco related diseases, e.g., cardiovascular disease, cancer, chronic lung disease, begin as inflammatory processes. Reduction of inflammation and oxidative stress may eventually lead to reduced disease risks. Use of THS appeared to reduce these processes to some degree during the studies, but, as noted, the data are not sufficient to show that these small changes are associated with long-term results.” **Comment:** How is this better for public health? |
| 59-61 | Clinical effects of IQOS. Looked at data and information to evaluate the short-term health risks of IQOS, including safety data reports from 8 completed clinical studies, two ongoing clinical studies, premarket safety surveillance covering 6 market research studies and one perception and behavior study, and post-market surveillance studies outside the US. Review included an analysis of adverse events (AE) in clinical studies and a review of published clinical literature. 717 AEs were reported, including 19 “severe” AEs. 121 AEs were reported in the actual use study, including 19 “serious” AEs. Headache was the most frequently reported non-serious AE. Severity was not reported in 50% of the cases. |
| 60-61 | Summary. The medical review noted the following limitations related to information about health effects of IQOS: (1) **the 8 clinical studies did not specifically evaluate the possible risks or benefits of dual/poly tobacco product use**; and (2) the reported AEs and compliance rates in a controlled clinical setting and small sample size may not be reflective of general use. Other AEs (including more severe) may occur with use by a diverse population.TPL agreed with medical review that there are limited data re short-term health effects of IQOS and even less data for longer-term effects. Nevertheless, TPL concluded: ***“Although limited, the data available in the clinical studies completed by the applicant do not raise concerns or identify specific health-related issues uniquely related to IQOS.”*****Comment**: The absence of evidence is not evidence of absence. |
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| 61-62 | **Likelihood of product misuse or malfunction.** |
|  | The Actual Use study assessed self-reported misuse of IQOS. Of 985 participants, 5% reported using the Heatstick without the device, 98% lit the Heatstick like a regular cigarette, one participant chewed the Heatstick, two used the device with marijuana. Several “device events” (does not charge, battery malfunction, heater broken) were reported, but were “relatively minor" and “did not impact subject safety.” There were no battery explosions or burns. A section about potential for consumers to attempt to re-use Heatsticks was redacted. (why??) No data was provided on whether consumers misused the holder by attempting to use a conventional combusted tobacco product (e.g., cigar or cigarette). TPL dismissed this, saying the levels of any HPHCs generated by using a CC with the IQOS holder would be lower than the HPHCs generated with usual use of a CC; additionally, most conventional US cigarettes would not fit smaller circumference. TPL concluded overall that despite limitations of self-report data, the study suggested that consumer misuse of IQOS device and Heatsticks is uncommon. Large redacted portion of conclusion apparently discuss how consumers could re-use a health or inappropriately use other CCs with IQOS holder.  |
| 62 | Bioresearch Monitoring Inspection (BIMO).Overall, BIMO inspection findings indicate the conduct of the US-based study at two clinical sites generally complied with study-related procedures. |
| 62-64 | 2017 Safety Update Report.In a letter dated 5/16, 2018, FDA received a PMI Safety Update report (SUR) summarizing safety info on IQOA for Jan. 1 – Dec. 31, 2017. **The SUR identified previously unrecognized short-term health risks associated with IQOS including hypersensitivity reactions, an accidental child exposure, and weather-related “hot aerosols” causing “burning sensations,” especially in the summer months.** A section of TPL’s assessment is redacted, but PMI seemed to respond by providing Customer Care agents with a “consumer communication script” reminding them not to expose the product to high temperatures and humidity.The Safety Update also reported battery leakage due to short circuiting and risks of thermal burns. PMI’s response to FDA’s request for clarification is redacted. Apparently, PMI developed an “‘improved’ THD [IQOS] 2.4” with modifications, but details about the modifications were redacted.The SUR (Safety Update Report) Supplement 1 reported **14 serious adverse events as cardiac disorders (e.g. angina pectoris, arrhythmia, myocardial infarction)**; however, “definitive conclusions could not be determined” about these. The SUR also reported one death in an 88-year-old, but this may have been unrelated to IQOS.TPL concluded: “The new AE safety information, including the unexpected death of the study participant, does not change the conclusion that *short-term risk of THS [IQOS] use is no greater than the risk of CC smoking*.”Even if you don’t think cardiac disorders such as MIs are significant health risks, this reasoning is another reflection of the inappropriate standard FDA is using – “no greater than the risk of CC smoking.” With this standard, as long as a new product is as deadly as cigarettes, but no more deadly than cigarettes, they can get new tobacco product authorization.  |
| 64-65 | **Summary of individual health findings from clinical studies, literature, adverse experience reports, and safety updates.** |
| 64 | “The medical review concludes that ***THS 2.2*** has the ***potential to benefit*** ***certain individuals*** seeking to ***reduce their HPHC exposure by completely switching from CC.”***(1) At page 63, report says that it is the “improved” “THD 2.4,” not “THS 2.2” that is the “subject of these applications and intended for US marketing.” So not the same product? (2) Note all the wiggly language: “*potential*” (not likelihood) to benefit, “certain” (not most or all) individuals, seeking to “reduce their HPHC exposure” (again, the “reduced exposure language, whether or not it’s true, and whether or not it reduces harm), in the users “completely switch” (not dual use) from CC. |
| 64 | “The review concludes that short-term health effectsdata from the clinical studies and additional longer-term information from published literature provided in the applications ***do not raise unique or additional health concerns or identify unique, specific health-related******risks for the IQOS system***.”Rationale for this conclusion:1. ***Reducing exposures to HPHCs*** through ***complete switching*** can potentially reduce the risk of adverse health effects ***compared to CC***
2. ***Data about BOPH are insufficient to draw meaningful conclusions about*** the ability of THS 2.2 to impact ***disease risk***
3. ***Clinical trial data about AEs*** related to THS 2.2 are limited but suggest that ***the short-term risk is no greater than risk from CC***
4. The relatively low incidence of serious and severe AEs in the international post-marketing surveillance SUR and the published literature suggest that switching to ***THS 2.2 may not increase the incidence of short-term adverse health effects for U.S. users relative to CC.*** However, the ***short-term AE data do not demonstrate a reduction in long-term health risk relative to CC.***
5. Again, language about “reduced exposures to HPHCs” as key factor; however, requires “complete switching” to “potentially” reduce risk of adverse health effects;
6. Also, problem with not considering all of the HPHCs (per Gideon St.Helen’s paper discussed related to page 11)
7. Despite noting insufficient data about biomarkers of potential harm, this does not influence ultimate decision;
8. Short-term risk is “no greater” than risk from CC again reflects the FDA’s low bar for approving IQOS This does not comport the public health standard required to be met to issue a new tobacco product order;
9. Dismisses short-term adverse health effects related to AEs, and says that data do not show a reduction in long-term health risks.

This finding does not support a conclusion that IQOS is “appropriate for the protection of the public health.” |
| 64-65 | TPL agrees with medical review’s overall conclusions.Says 5-day studies show reduced HPHC exposures indicated by improved BOE “in those that completely switched” to IQOS. Said trends continued in 90-day studies, but reduced compliance and use of other tobacco products.“As TPL, I agree with the medical review overall conclusions. The 5-day studies demonstrate improved BOE in those that completely switched to THS 2.2, which indicates reduced HPHC exposures. These improvement trends persisted in the 90-day studies despite reduced compliance and use of other tobacco products. The currently available evidence indicates CC smokers who switch completely to IQOS will have reduced toxic exposures and, consequently, although not demonstrated in the studies in the application, are less likely to be at risk of tobacco-related diseases…. the limited available information shows trends, although not statistically significant, toward reduced HPHC exposures in this population.” The tobacco companies would never let the health groups get away with talking about non-significant trends.  This is the point of my paper in UC and the associated public comment.***“Although not demonstrated in the studies in the application,”*** TPL concludes that “currently available evidence indicates that CC smokers “who switch completely to IQOS’ will have reduced toxic exposures and, consequently, are less likely to be at risk of tobacco-related diseases.Even though the information submitted to FDA did not make the required demonstration, FDA apparently used “other information” to reach its conclusion. TCA section 910(c)(2) says FDA shall deny an application if “upon the basis of the information submitted to the Secretary as part of the application and any other information before the Secretary with respect to such tobacco product…” PMI submitted a “late amendment” with additional health effects. “In this study, CC smokers who use IQOS while continuing to smoke (***dual use***) do not appear to have increased HPHC exposures***; the limited available information shows trends, although not statistically significant, toward reduced HPHC exposures in this population.”***FDA is relying on data that is not statistically significant to demonstrate reduced HPHC exposures with dual use. The tobacco companies would never let FDA (or any health group) get away with this if the lack of a significant finding hurt the industry’s interests. |
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| **65-84** | **F. Population Health** |
| 66-67 | Table 5 – Summary of pre- and post-market studies of IQOS use patterns among current tobacco users |
| 67-68 | Limitations of design features of two pre-market studies that may have influenced the findings:* Observation periods were only 4-6weeks, so can’t discern if IQOS use patterns were sustainable over time
* Both studies provided IQOS to participants at no charge
* Participants in one study were shown labeling and marketing materials with MRTP info prior to making their decision about “interest” in IQOS
* These studies are not generalizable to US cigarette smokers, including different cultural contexts and differences in the availability of e-cigs or other HTPs
* Potentially overestimated the prevalence of IQOS use and estimates for initiation of IQOS and switching to IQOS, while estimates for switching from IQOS back to CC would be underestimated.
 |
| 68 | FDA’s statistical reviewers only assessed descriptive statistics, and “statistical inference was not part of the conclusion-making process.” |
| 68-72 | Likelihood of IQOS use, comprehension, and risk perception by current cigarette smokers, former smokers, never smokers, and young adult never smokers after exposure to OQOS labels, labelling, and marketing materials. |
| 68-69 | Limitations: 1. “As the applicant acknowledges, self-reported intentions to use products are limited in terms of predicting behavior and can overestimate the likelihood of purchase, particularly when participants’ responses have no consequences. For example, although participants viewed price information about IQOS and Heatsticks, they were not asked to make a choice between the product and money.”
2. Participants in the study do not constitute a representative sample of the US population. (However, FDA’s statistical reviewers “were able to replicate the statistical analysis provided by the applicant.”
 |
| 69 | In Actual Use (PBA-07) pre-market study of current CC smokers in US using self-reported data on the use of IQOS in a “real-world” situation to measure prevalence of initiating IQOS use, switching from CC to IQOS, and switching from IQOS back to CC:* prevalence of initiating IQOS use was 33.8% (lowest in US);
* prevalence of switching to IQOS was 32.7%;
* prevalence of switching back to CC was 15.5% (highest in the US);
* among those who initiated IQOS use, only 16.3% were “exclusive” IQOS users at the end of study;
* “switched to IQOS” = Heatsticks were 70% or more of total product use during last week
* “exclusive IQOS use” = Heatsticks were 95% or more of total product use during last week
* “switched back to CC” = Heatsticks were less than 30% of total consumed in a week after having switched to Heatsticks in an earlier week

“In the U.S. Actual Use study, 62.7% of participants were classified as predominantly CC users in the last week of the observational study period; however, among those who initiated IQOS use, 16.3% were “exclusive” IQOS users at study end. Other countries’ “exclusive IQOS use rate” at study end varied from a low of 7.8% in Switzerland to a high of 21.5% in Japan.”This shows that most IQOS users are dual users, something that the FDA does not meaningfully engage. |
| 70 | Table 7: prevalence of Heatstick trial and switching at study end“Less than 20% of smokers who switched to IQOS (≥70% Heatstick use) switched back to predominantly using CC (≤30% Heatstick use).”70% is not "switching".  It is dual use.  FDA should not be allowing PM to get away with this. |
| 71 | Figure 9: Likelihood of Heatstick purchase |
| 71 | Conclusion: Finding in Actual Use study that 34% of US cigarette smokers initiated IQOS use suggests that some smokers will find IQOS appealing and acceptable enough to initiate use of the product. However, since participants had to express interest in using IQOS prior to study enrollment, study participants may be more likely to find the product appealing than smokers in the general population, leading to overestimation of the prevalence of IQOS initiation among smokers.**Comment**: So among participants who had to express interest in using IQOS prior to enrolling in the study, and who were given free IQOS devices and Heatsticks, 66% did not end up initiating IQOS. FDA acknowledges that this may be overestimating prevalence of initiation, but does not act on this fact. |
| 72-73 | Poly-use of IQOS and cigarettes or other tobacco products. |
| 72 | PMI defined “dual use, ‘combined use’” as using 30-70% Heatsticks out of the total number of CC and Heatsticks per week. Using this definition, 57.6% of participants were dual users.**Comment:** Dual use was common. And 70% is still dual use.  |
| 72 | An “alternate definition” of dual use is using 5-95% Heatsticks out of the total number of CC and Heatsticks per week. Using this definition, 22.4% of participants were dual users. |
| 72 | When using PMI’s definition for “switching (≥95% Heatstick use), only 7.5% of participants in study met the criteria for switching.**Comment:** This statement shows that there was low real “switching.” |
| 72 | Most smokers were dual users during 6-week observational period, but report suggests that with additional time, more participants might have become “exclusive” (≥95%) Heatstick users  |
| 73 | PMI said that despite high proportion of dual users, there was a reduction the average daily cigarette consumption. FDA found that participants appeared to reduce by about 1 CPD and added about 2-4 Heatsticks per day. Therefore, they may be using more total units of tobacco products (CC and Heatsticks). Also, Heatsticks were provided free of charge, so use pattern may not accurately reflect general use pattern.“Accordingly, even though the average daily total appears relatively stable, participants may be using more total units of tobacco products when both cigarettes and Heatsticks are considered.” So total consumption went UP. This is not appropriate for the protection of the public health. |
| 73 | Data from a 2016 Japanese on-line post-marketing survey showed 3.7% of respondents used HTPs, and the prevalence of HTP use was about 4 times higher among people aged 20-39 (4%) than those aged ≥40 (1-1.5%). **Among respondents who used HTPs, 84.9% also smoked cigarettes, most of them daily. In total, 91.8% of HTP users reported dual use with at least one other tobacco product**.  |
| 73 | Notes that although PMI used data from Japan, e-cigs require a prescription in Japan, so data may not be generalizable to the US population. |
| 73 | In conclusion: “**Dual use of CC and IQOS appears likely.** There is **concern about the effects that dual use of IQOS and CC (compared to complete switching) will have on long-term reduction of HPHC exposures and the health risks for tobacco-related diseases.** While results from the PBA-07 study showed that IQOS use was associated with reduction in cigarette consumption, **the health benefits of reducing cigarette consumption instead of quitting completely are unclear.****Comment**: This is not an improvement in public health. FDA’s recognition of likely dual use should have led them to deny the application. |
| 73-76 | Use of IQOS by former or never smokers and youth. |
| 74 | “It is likely that Risk Perceptions are primarily based on factors such as the appearance of the THS device (which is similar to some e-cigarettes) and the impression that the product is innovative and new. These perceptions related to similarities between IQOS and e-cigarettes may be important when considering potential appeal among people who do not currently smoke.”  |
| 74 | Brochure includes statement that IQOS is intended for smokers and not intended for non-smokers, and Heatsticks would be marketed under the Marlboro brand name. Since they are cigarette products, they won’t be marketed with flavors. Since flavors is a commonly-cited reason for never smokers’ use of e-cigs, these characteristics may reduce the appeal to nonsmokers. |
| 74 | Study limitation: never smokers, including young adults (legal age to 25 years) were only exposed to regular Heatsticks, not menthol, despite knowing that menthol cigarette smokers comprise 1/3 of US market, and more than half of those who smoked for the first time initiated with menthol cigarettes. |
| 75 | When “somewhat likely” are included in estimates of positive intention to use IQOS, 4-7% of never smokers and 7-11% of young adult never smokers reported an intention to try IQOS, and 17-25% of former smokers reported an intention to try IQOS, with 7-14% reporting an intention to use regularly if they tried IQOS and liked it.**Comment:** These are big numbers indicating high risks of expanding tobacco use, which is not appropriate for public health. |
| 75 | PMI did not include bridging information on youth use (under 18), or youth use of other products (cigarettes, e-cigs), which might have helped FDA better understand youth intentions and perceptions re IQOS. |
| 75 | “Among survey responders in 2017, there were 3.6% current IQOS users and 2.0% of those aged 15-19 years reported current use of IQOS in 2017. Of the 2017survey responders 1.3% were never smokers, 2.1% were former smokers, 18.8% were current smokers with intention to quit, and 10.3% were current smokers with no intention to quit.” **Comment:** Again, these are big numbers. They could expand product use by 10%, which is a lot. |
| 76 | In a 2017 post-market Japanese survey, 2% of youth aged 15-19 reported current use of IQOS.“The PBA-05 study also suggests a low prevalence of intention to use IQOS among never smokers.”**Comment:** As noted above, the never smoker numbers are not small when compared to smoking prevalence. |
| 76 | Conclusion: prevalence of IQOS use is lower in never smokers compared to current smokers and fewer youth than adults currently use IQOS in Japan or Italy. In countries where IQOS is marketed (Italy and Japan), low uptake by youth and current nonsmokers. Low prevalence of intention to use IQOS among never smokers, and slightly higher, but still low, in former smokers. PMI noted that data are less sensitive for less decisive responses (e.g., “somewhat likely”). |
| 76 | Report notes that “certainly, the potential for rapid uptake of a novel tobacco product among youth exists” (noting rapid rise of youth use of e-cigarettes); however, said “limited flavor choices may reduce IQOS’s appeal to youth,” as well as the price of the IQOS device. “Overall, the current evidence indicates IQOS uptake by youth and nonsmokers will be low.”This conclusion is contradicted by the peer reviewed paper on how IQOS, HTPs likely appeal to adolescents and young adults:McKelvey K, Popova L, Kim M, et al. Heated tobacco products likely appeal to adolescents and young adults. Tob Control. 2018;27(Suppl 1):s41–s47. doi:10.1136/tobaccocontrol-2018-054596Also, what is the price of IQOS compared to the price of Juul? (Juul starter kit is sold on juul.com website for $44.99 as of May 7, 2019, but this “limited time offer… reflects $20 off.) <https://www.juul.com/shop/devices/starter-kit>$48.95 here: <https://www.electrictobacconist.com/juul-starter-kit-p833>Device kit costs $34.99. <https://www.juul.com/shop/devices/silver-device-kit> (does not include pods)While the FDA cannot regulate price, price will affect use patterns, which will affect the population health impact.**Also, recent Reuters report on PMI using young influencers to market IQOS flies in the face of these arguments that IQOS doesn’t or is not intended to appeal to youth.** In any case, if IQOS does not currently appeal to youth, looks like PMI is doing whatever it can to change that… |
| 76-77 | **Likelihood of IQOS leading to conventional cigarette smoking cessation** |
| 77 | Results of two studies show that “most smokers become dual users or at least go through dual use phase before quitting.” |
| 77 | Results of post-market study in Japan were better, but report notes that since nicotine containing e-liquid is categorized as a pharmaceutical ingredient in Japan and nicotine-containing e-cigs are not as readily available in Japan as in the US, these results may not be generalizable to the U.S. “In the Japanese post-market study of IQOS purchasers who registered their device in an online database, 52%-65% of IQOS purchasers were considered exclusive IQOS users. However, those who take the initiative to register their device are likely to be a non-representative sample of all Japanese IQOS users and may be more motivated to become exclusive IQOS users.” **Comment:** This is more evidence of high dual use.Less than 10% of cigarette smokers in the US study switched to exclusive IQOS use. **Comment:** More evidence of high dual use.Nevertheless, because “the proportion of exclusive IQOS users remained steady during the 6-week observational period, report concludes that “individuals who initiate IQOS and use Heatsticks for at least 95% of their tobacco intake are able to maintain exclusive IQOS use over time and potentially replace their use of CC with Heatsticks long-term.” |
| 77-79 | **Population modeling** |
| **77** | **Initial population in the model scenarios is representative of the US in 1990.** 1990 is about 17 years before e-cigs were marketed in the US, and almost 30 years before the Juul explosion. Can assumptions based on this population be valid today? For example, it assumes that within 10 years of being on the US market, new tobacco products will be used by 17% of US smokers. It also **assumes that “Most current cigarette smokers transitioning to the new products will be middle aged;** younger people are less likely due to cost and older people are generally less likely to switch. But we know that 20% of high school kids reported using Juul in 2018. **It also assumes that approximately 15% of new tobacco product users will be exclusive users and only 2% will be dual users with cigarettes.** What is the percentage of dual use today? |
| 78 | Based on these assumptions, the applicant concludes that IQOS would lead to a “sizeable public health benefit in term so reduced cigarette smoking and tobacco-related mortality.”There are huge problems with this model, which is documented in Wendy Max’s paper in the IQOS supplement and in her public comment that the FDA ignores.Paper: Max WB, Sung H, Lightwood J, et al., Modelling the impact of a new tobacco product: review of Philip Morris International’s Population Health Impact Model as applied to the IQOS heated tobacco productTobacco Control 2018;27:s82-s86.Public Comment: Max WB, Lempert L, Sung H, et al., Philip Morris’s Population Health Impact Model Based on Questionable Assumptions and Insufficient Health Impact Measures Does Not Adequately Support its MRTP Application, November 22, 2017. Docket Number: FDA-2017-D-3001, Tracking Number: 1k1-8zy0-6rfg. Available at: <https://www.regulations.gov/document?D=FDA-2017-D-3001-0121> |
| 78 | FDA noted that the model considers deaths from four conditions (lung cancer, COPD, ischemic heart disease, and stroke), which account for 336,000 of 437,000 deaths directly attributable to cigarette smoking, but does not account for deaths from secondhand smoke exposure due to IQOS use. Also, prevalence estimates for CC smokers is too high, so model overestimates current smokers at baseline compared with present and overestimates any population health impact of smokers switching to another product. See problems with model documented in Wendy Max’s paper and public comment cited above. |
| 78 | Report says model does not present empirical evidence supporting forecast that 17% of smokers in US population will use IQOS in 10 years and 30% will use IQOS in 20 years. Therefore, “If uptake of the products by consumers is lower, takes more time, or is more likely to occur as part of dual use, then the magnitude of any population health effects would be expected to be reduced.” Also, report notes that exposure among dual users may not be the average of exposure of exclusive cigarette and IQOS users. Also, individual harm from exposure to exclusive or dual use with IQOS may not follow a linear dose-response relationship.See problems with model documented in Wendy Max’s paper and public comment cited above. |
| 79 | Notes limitations to the PHIM modeling assumptions, input data construction, and inference procedures. Model only consider two products – cigarettes and IQOS. **The model should have considered e-cigs, which industry and the FDA maintain are associated with fewer population health impacts than cigarettes, the current comparator for IQOS.** |
| 79  | Report says, “The applicant provides very little justification and no specific empirical evidence to support the assumptions that individuals who do not currently smoke cigarettes would not be interested in using the proposed products or that young people would not find them appealing.” |
| 79 | Report says, “the relatively short projection period of 20 years and use of mortality as a health outcome does not allow for adequate consideration of the long-term health effects of tobacco use initiation among youth and youth adults.”  |
| 79 | Because the FDA ignores Wendy Max’s paper (discussed above), the FDA concludes: “There are no major concerns with the statistical and computational aspects of the PHIM...”“The applicant provides very little justification and no specific empirical evidence to support the assumptions that individuals who do not currently smoke cigarettes would not be interested in using the proposed products or that young people would not find them appealing... The projected population health effects of the proposed new tobacco products may be overstated if specific assumptions about tobacco use behavior and risks are not realized in the actual population. **Although the model is statistically valid, the overall analysis of the population model does not provide evidence to support the application”.** **Comment**: Although FDA concluded that for various reasons, the model overstated health benefits to the actual population and does not provide evidence to support the application, it still authorized sales. As noted above, FDA also ignored all the criticisms in Wendy Max’s paper, which are significant. |
| 79-83 | June 11, 2018 amendment to MRTP considered in this PMTA application.RCT of ad lib use of non-menthol IQOS by 984 health adults (mean age 44.6) compared to continued CC users. Objective of study was to demonstrate favorable changes after 6 months across 8 clinical risk endpoints (BOPH) for those switching from CC to IQOS compared to continued CC use.  |
| 80 | Primary study results: “Five of the eight endpoints showed a statistically significant change in smokers who switched from cigarette smoking to THS use. All BOPH shifted in the direction seen when smokers quit.”  As discussed above regarding page 11, PMI relied on little-used methods that are highly subject to manipulation.FDA also ignored the fact that PMI’s originally submitted clinical data failed to show statistically significant changes in most of the clinical variables PMI measured:Paper: Glantz SA, PMI’s own in vivo clinical data on biomarkers of potential harm in Americans show that IQOS is not detectably different from conventional cigarettesTobacco Control 2018;27:s9-s12.Public Comment: Glantz, SA. 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, November 13, 2017, Docket Number: FDA-2017-D-3001, Tracking Number: 1k1-8zrx-juh9. Available at: <https://www.regulations.gov/document?D=FDA-2017-D-3001-0108> |
| 81 | Table 10 – primary analysis of clinical risk endpoints between IQOS use and CC use at 6 months. (Values were one-sided p-values) |
| 81 | Secondary study objectives; evaluate self-reported product use (IQOS or CC) and nicotine exposure levels, and **evaluate exposure** reduction to selected HPHCs (BOE) in dual use and IQOS use groups. |
| 81 | Figure 10 – report says it shows “significant reductions in exposure levels in the THS group and the dual use group,” and says, “the applicant believes these results confirm that THS 2.2 can deliver nicotine at levels comparable to CC and that adult smokers can accept THS as an alternative to CC.” |
| 82 | Applicant concludes that up to 30% “concomitant use may occur, and this could reduce the risk reduction potential of THS.” Also, applicant notes that the primary study object was met and HPHC exposures were reduced, even with the concomitant use pattern.” |
| 82 | 19 serious adverse events were reported by 13 subjects in the study, but none of the serious AEs was believed related to IQOS or CC use. Two deaths: one was caused by acute and chronic alcohol abuse, and the other a self-inflicted gunshot wound. Additionally, 415 subjects reported 758 AEs. The most common AEs were upper respiratory tract infections (4.3% in IQOS, 4% in dual use, 6.2% in CC). |
| 82 | Applicant’s conclusions:􏰜Applicant’s Conclusions: * 􏰜Among􏰉subjects randomized to use THS, 34%used THS exclusively (defined as 􏰭􏰁≥95% use). Another 34% dual-used THS and CC. The applicant believes these results show the product was well accepted considering that before switching, subjects were naive to the product.
* Overall, all the clinical risk endpoints (BOPH) evaluated in those switching from CC to THS followed the same direction as seen following smoking cessation. The changes were statistically significant in five of the eight BOPH measured.
* In addition to NNAL and COHb measured as BOPH, eight BOE were assessed. In all cases, there was significant reduction in THS users compared to CC users.
* 􏰧Exposure to nicotine was comparable between THS and CC users.
* 􏰣With respect to dual use (defined as subjects whose THS use was 1-70%):􏰏

o 􏰛BOPH showed a shift (although minor and not generally significant) in the favorable direction at six months compared to CC use.  o 􏰛BOE showed slight reductions compared to CC at six months (2.6-13%)   |
| 82-83 | FDA notes limitations to applicant’s statistical approach:* study was ambulatory, not controlled clinical trial (as characterized by applicants); study did not this didn’t affect data validity.
* Because of the way applicant used modified groups for the primary analysis, eliminating about 50% of participants which “breaks the initial balance between the IQOS and CC study arms obtained via randomization,” significant differences between the IQOS and CC study arms may be due to factors unrelated to the exposure
* Although the data analyses assumed that the changes in BOPH (the individual outcomes) are independent for each of the 8 primary biomarkers, this is unlikely, since the selected BOPH are affected by multiple factors, including general health, other medical conditions, infections, genetics, age, diet, exercise, and medications. “Nonetheless, the measured changes in BOPH are valid, even if not independent”
* Applicant provided no scientific justification suggesting that BOE and BOPH related to CVD, cancer, and lung function are appropriate to combine as an overall metric of clinical significance.
* Because the study arms became imbalanced at the 6-month time point, the use of multiple comparisons performed with the Halperin-Ruger statistical method is not justified.
 |
| 83 | Overall conclusion: **“due to limitations in design and statistical analysis, no definite conclusions can be made based on this study. *However, despite these limitations, the study provides evidence of reduced exposures associated with switching completely from CC to THS.”*** Additionally, those with self-reported dual use “had no evidence for increased toxin exposures.” The rate of self-reported dual use in this study (34%) was lower than considerably higher dual use rates in previous studies (58%). Rate of adverse events “was similar” for those exposed to IQOS and CC. Nicotine exposure levels were also comparable between IQOS and CC.FDA TPL: “Because the study arms became imbalanced at the six-month time point, the use of multiple comparisons performed with the Halperin-Ruger statistical method is not justified. Due to limitations in design and statistical analysis, no definite conclusions can be made based on this study.”Despite this finding by the TPL that “the Halperin-Riger statistical method is not justified,” FDA accepted the results based on this method. A conventional analysis of PMI’s results would show no significant differences between IQOS and CCs for most of the measures. |
| 83-84 | Summary of Population Health Findings |
| 83 | The social science review concluded that they had “concerns” about a number of issues in the application:* Lack of information about youth under age 18
* Lack of discussion of data’s applicability to youth and lack of stratified data that would enable reviewers to make inferences about youth
* Potential for initiation among young adult never smokers
* Potential for dual use among current smokers, with only a one cigarette per day decrease in use frequency
* Taken together, the PMTAs do NOT contain sufficient information to address these social science concerns
 |
| 83-84 | **TPL said they did NOT agree with social science conclusions:*** Said there was “limited data,” rather than “no data,” on use and possible uptake in youth, and cited Japanese and Italian studies that show low uptake by youth and current nonsmokers, concluding overall that the current evidence indicates “low IQOS uptake by youth.”
* Agreed there are concerns about dual use. However, were reassured by PMI’s stated intention to market IQOS “for adult smokers who wish to completely switch,” and limited data showing that “a dual use period is common during the switching period, but those who switch ‘quickly and completely’ were more likely to successfully remain off CCs.”
* Also, TPL pointed to data that “HPHC exposures are not increased in those who dual-use IQOS and cigarettes,” and that HPHC reductions continue through the extended exposure studies even when participants were not in controlled environments and dual-use was likely.
* Also, “although the changes were not statistically significant, the 6-month study showed decreases in BOE for dual users as compared to exclusive CC users.
* Noted that **PMI’s studies did not demonstrate reduction in long-term disease risk; however, the reduced exposures combined with other available information led TPL to conclude *that IQOS is appropriate for protection of public health, even if there is some dual-use among smokers as they potentially transition to the product.”***

Despite the TPL’s many enumerated concerns, **FDA rejected its own experts' conclusions that the social science evidence does *not* support IQOS.**Once again, TPL relies on **reduced exposures** to excuse other problems in the PMTA applications, just about ensuring that FDA will authorize MRTP for reduced exposures. |
| 84 | Epidemiology review **concludes that the applicant has demonstrated that the *exclusive use* of IQOS exposes users to substantially lower exposure to many HPHCs compared to smoking CCs**. * recommends requesting post-marketing info on differences in BOE in CC smokers that completely switch to IQOS compared to those w dual use with CC.
* also recommends evaluation of the 53-62 compounds found at higher levels in the aerosol compared with cigarette smoke
* also recommends long-term evaluation assess changes in BOPH and clinical endpoints associated with complete and incomplete switching

TPL: “Additional clinical evaluation of the 53-62 compounds found at higher levels in the aerosol of the products that are the subject of these applications compared with cigarette smoke would also be helpful for supporting􏱇continued marketing􏱇of the products as appropriate for the protection of public health. **Comment:** FDA is ignoring these red flags in the application. |
| 84 | TPL review agrees with epi review conclusions, and agrees with recommendations for requesting continued information on toxic exposures as products are actually used, as well as information on long-term health effects.Astonishingly, FDA basically acknowledges problems with incomplete switching and dual use, but decided they will look at post-market data to see how it goes in the future. This is similar to how they are handling e-cigs: Sit quietly while they addict tons of kids, rather than applying the law as written, especially the public health standard. |
| 85-90 | **III. Product labeling, consumer comprehension, and marketing plan** |
|  | This section contains many redactions, many of them large (e.g., the marketing plan) |
| 86 | FDA notes that because statistical inference was not the basis for informing the conclusion-making process in the submitted study, the results are not generalizable to the US population. Nevertheless, report concludes that the results demonstrate sufficient consumer understanding of the products and their use. |
| 86 | “Additionally, the applicant has stated their intent to [redaction]. The additional support along with the instructions that are included with the IQOS device should resolve most consumer issues related to product use.”We assume the redacted portion describes PMI’s planned marketing and/or “support” activities, which may be through two-way communications in the chip, or the “hands on” customer support approach described at the TPSAC meeting whereby PMI reps will call customers directly to help them learn how to use the product/ (buy more stuff?!). |
| 86-87 | Marketing plan – redacted.  |
| 87-89 | Nicotine is addictive labeling |
| 87-88 | TPL: “These findings raise concerns because they indicate that consumers, including young adult never smokers, do not fully comprehend the addiction risk of IQOS based on the currently proposed labeling, which does not include any information about nicotine or addiction. Of further concern is that consumers, including􏱇young􏱇adult never smokers, who mistakenly believe IQOS to be less addictive, may start using it when they would not have otherwise initiated tobacco use.” Because of concerns that consumers, including young adult never smokers, do not accurately perceive the risk of addiction associated with IQOS use, which could have negative public health consequences in terms of increased initiation among nonusers and decreased cessation among tobacco users, TPL recommends requiring inclusion of the nicotine warning on all IQOS Heatsticks labels and in all IQOS advertising “WARNING: This product contains nicotine. Nicotine is an addictive chemical.”The problem is that this is not an effective warning when it comes to actual communicating, particularly with youth.TPL recommends that the warning be subject to the same format requirements as those currently required for the nicotine warning on covered ENDS products under the deeming rule.A crucial omission is that the warning is NOT required on the device which is the point of initial purchase and the thing with the fancy marketing and packaging.  This is a serious shortcoming. |
| 89 | Recommends that warning be subject to the same format requirements as those currently required for the nicotine warning on e-cigs. (at least 30% of 2 principle display panels of every Heatstick package or kit with Heatsticks, and occupying at least 20% of the area of every print or other ads (e.g., web pages) with a visual component. |
| 89-90 | Carbon monoxide warning |
| 89 | As cigarettes, IQOS Heatsticks require rotating surgeon general warnings, one of which states, “Cigarette Smoke Contains Carbon Monoxide.” |
| 90 | PMI provided evidence that although Heatsticks do produce CO, the exposure to CO from IQOS use “is comparable to environmental exposure to CO.” Based on evidence in studies, TPL concludes that use of Heatsticks in the IQOS device does not pose any CO-related risks. Therefore, the CO warning is “misleading with respect to IQOS products,” and this warning should NOT be required on IQOS packaging or advertising. |
| 90-107 | **IV. Conclusions and Recommendations.** |
| 90-98 | Summary of information and studies provided in applications. |
| 91-92 | Toxicological assessment – concludes that 54 HPHCs measure in Heatstick aerosols were reduced by 54.4-99.9% on a per stick basis when compared to 3R4F smoke. Machine-generated nicotine yields were reduced 35.9-39.4%, but clinical data show human CC smokers and IQOS users absorb similar amounts of nicotine.For 18 compounds, PMI said yields in aerosols were reduced by 40-99.8% compared to the mean of 31 CCs commercially available in the U.S.Sidestream aerosol levels are significantly lower that CC emissions.**Heatstick aerosols contain higher levels of some chemicals that 3R4F smoke, four of which are possible or probably carcinogens and 15 others are possibly genotoxic. *However,*** TPL concludes that based on current knowledge, ***the toxic exposures from all three Heatstick aerosols are reduced compared to CC, and many of the known HPHCs found in CC smoke are very low or undetectable in Heatstick aerosols.*** |
| 92 | Notwithstanding limitations of in vitro testing assays, overall they show decreased cytotoxicity and mutagenicity from exposure to TPM and GVP of IQOS compared to that of 3R4F cigarettes. This is consistent with expected results from aerosol containing the amount of HPHCs identified in studies. |
| 92 | In vivo inhalation studies in rats and mice on carcinogenicity, nicotine pharmacokinetics, and systems toxicology showed changes from Heatstick aerosol exposures were not observed or were much less severe than changes due to 3R4F. An interim report of an 18-month carcinogenicity study showed neoplastic lesions to be higher in IQOS-exposed group or CC compared to sham control; however, the final study report concluded no increase in lung cancer risk due to IQOS aerosol exposure compared to the sham control group. Applicant said the toxicity is limited to adaptive responses in the upper respiratory tract. “As an inhaled tobacco product, IQOS may elicit an inflammatory response in the respiratory tract, but this study provides no definitive information about carcinogenicity risk for humans.” |
| 92 | Considering all the toxicological data presented, “the demonstrated reductions in measured HPHC exposures and reduced histopathological changes indicate a possible relative benefit compared to CC for smokers who switch completely to IQOS.” |
| 92 | Although IQOS aerosols contain chemicals which are different from those found in CC, some of which may be toxic, the currently available information indicates that the reduced exposures to the large number of HPHCs found in CC will likely result reduced health risks for CC smokers who switch completely to IQOS. Reduced HPHC exposure also is beneficial for those who would be secondarily exposed to IQOS aerosol as compared to secondhand tobacco smoke.Once again, reduced exposures to HPHCs win the day despite the fact that the more important measures of clinical effects on users do not support a conclusion of reduced risks, the thing that matters in terms of determining whether approving IQOS would be appropriate for public health. |
| 93 | PK/PD study results show that PK in smokers who switch to IQOS is similar to those who continued to smoke CC. The data indicate that IQOS “has addictive potential and abuse liability similar to CC which means that while IQOS can provide an adequate nicotine source for dependent populations, there is a risk of developing addiction for non-tobacco users who begin using IQOS.”Despite data showing IQOS may have similar addictive potential and abuse liability to CC, and therefore risky for non-users, still TPL concludes that benefits to smokers who “switch completely” outweigh risks to non-smokers. |
| 93 | In reduced exposure or “REX” studies, systemic exposure to 15 of 16 selected chemicals decreased by 47-96%. However, nicotine (also an HPHC) was measured and levels were not decreased. “These BOE reductions in those that ***completely switched to IQOS*** indicate reduced HPHC exposures, and – ***although not demonstrated by the studies in the application*** – these reductions in exposure are likely to result in reduced risk of tobacco-related disease.”“Some BOPH had desirable change trends in THS 2.2 users compared to the CC arm, but only white blood cell (WBC) count and slCAM-1 demonstrated differences in the two 90-day studies for THS 2.2, CC, and SA arms. The BOPH measures were not significantly improved over the relatively short duration of these studies; however, the trends may be informative for understanding potential effects on biological processes such as inflammation and oxidative stress.”So, what the application shows is no benefit.  FDA is speculating that there *might* be benefits in the future. It is hard to see how this speculation can be used to support a decision that allowing IQOS to be marketed would be appropriate for public health. This is another place where FDA is prioritizing giving PMI the benefit of the doubt, rather than prioritizing public health by requiring PMI to demonstrate that marketing IQOS would improve public health. |
| 93 | After independent review of the literature on BOPH, FDA concludes that while each of 6 markers have data suggesting a relationship with one or more tobacco-related diseases, none were strong predictors of future health risks. (Notes longer term studies are needed.) |
| 93 | Although applicant determined that most of the reported adverse events were unrelated to product use, IQOS exposure cannot be ruled out as contributing to or exacerbating those AEs typically associated with tobacco exposure (e.g., cough, headache, syncope). |
| 94 | A Safety Update report published in April 2016 reported two serious adverse events (nervous system disorders/syncope). A May 2018 Safety Report identified previously unrecognized short-term health risks associated with IQOS including hypersensitivity reactions, an accidental child exposure, a weather-related (heat and humidity “burning sensation.” Applicant reports that [redaction], which improvements/modifications are expected to decrease the occurrence rate of AEs, and are “consistent with the conclusion that short-term risks of IQOS e are no greater than those associated with CC.”**Comment**: Authorizing the marketing of a product that creates risks that are no worse than those associated with conventional cigarettes is not how to read the public health standard. |
| 94 | Report of acute eosinophilic pneumonia in a young adult Japanese male after increasing consumption of IQOS dismissed as not “beyond the concerns of CC use.”“The data available in the clinical studies and other submitted information do not identify specific health-related issues for IQOS use beyond the concerns of CC use.”Again, the FDA is saying that IQOS is ok if it is no worse than a CC.  That is not a public health improvement. |
| 94 | A June 2018 amendment included data from a six-month ad lib study of IQOS compared to CC in an ambulatory setting in the US. Five of 8 BOPH endpoints showed a statistically significant change in smokers who switched (defined as ≥70% IQOS use) from CC smoking to IQOS use. All BOPH shifted in the same direction as when smokers quit, and users who switch to IQOS (≥70% IQOS use) had reduced levels of BOE for most measures. Dual users (defined by PMI as 1%-70% IQOS use) had reduced BOE for most measures, but the changes were smaller and not statistically significant.This is the same study they talked about earlier on page 11 where the FDA said the statistics were not done appropriately on page 83.  In fact, FDA makes that point in the next paragraph. The conclusion that the FDA is drawing is inconsistent with the conclusion it draws on page 83 that the Halperin-Ruger statistical method is not justified since the only way to get the conclusion is to use the inappropriate statistical method. |
| 94 | None of the BOE measures increased with IQOS use – even in those who were “dual users” in the study. |
| 94 | Notes limitations to PMI’s statistical approach that affect the reliability of the statistical conclusions of the study. “However, the study does provide evidence of reduced exposures associated with switching completely from CC to THS.” Additionally, there as a trend for BOE reduction in dual users. |
| 95 | Although the short-term and long-term effects of dual use remain unclear, these data provide “minimal evidence” that short-term dual use of IQOS and cigarettes does not appear to increase exposures to the *selected* HPHCs. |
| 95 | Overall conclusion: the clinical studies show exclusive use of IQOS has “***potential”*** for reduced adverse effects on individual health compared to CC smoking.**“The currently available evidence indicates CC smokers who switch completely to IQOS will have reduced toxic exposures and, although not demonstrated by the studies in the applications, consequently, are likely to have less risk of tobacco-related diseases.”** **“CC smokers who use IQOS while continuing􏰄to smoke (dual use) do not appear to experience increased HPHC exposures and the limited available information indicate they may also have reduced HPHC exposures.”** |
| 95 | Perception study, actual use study, and WOT study assessed likelihood of IQOS use by current CC smokers. Varied results. |
| 95 | ***“Dual use of IQOS and CC was common”*** (57.6% dual use) in all countries in the pre- and post-market studies. “Among current smokers in the actual use study, a majority (57.6%) used the IQOS in addition to conventional cigarettes when dual use is defined as between 5% to 95% Heatsticks.” |
| 95-96 | Less than 8% switched completely (≥95% IQOS use) from cigarettes to IQOS. |
| 95 | Lucy Popova’s reaction: Another thought that occurred to me as I was reading the conclusions is that the report's conclusions on the likelihood of use are based on the studies that were submitted as part of the MRTP application. "The likelihood of IQOS use by current CC smokers was assessed in the perception study, the actual use study, and the WOT." (p. 95). At least in the perceptions studies, the likelihood of use was assessed based on marketing with the modified risk statements (as I recall they did not have a control condition that could be comparable with the no-MRTP marketing that will be happening now). So the estimates of smokers being interested in switching is based (at least in the premarketing studies) on claims with MRTP statements. This might (but likely not) translate into actual interest under the marketing without MRTP claims.  |
| 96 | **Concern since there is limited evidence about the effects that dual use of IQOS and CC (compared to complete switching) will have on long-term reduction of HPHC exposures and the health risks for tobacco-related diseases.** The health benefits of reducing cigarette consumption instead of quitting completely are unclear. However, TPL concludes based on currently available evidence that “dual use is unlikely to pose increased health risks compared to contend exclusive CC use.” |
| 96 | A 2016 Japanese post-market study showed prevalence of HTP use was higher among those aged 20-39 than those aged at least 40. Among HTP users, 84.9% also used CC, most of them daily.The proportion of IQOS purchasers who were “exclusively” using IQOS (≥95%) increased from 52% in January 2016 to 65% in July 2016.”This is still a lot of dual users. |
| 96 | In US perception study assessing perceptions and intention to use IQOS among former and never smokers, including a subgroup of young adults (aged 18-25), labeling and advertising materials provided information intended to distinguish IQOS from e-cigs. **Never smokers in this study, including young adults, were only exposed to regular Heatsticks, not menthol. This is a study limitation, since one-third of cigarette smokers in US use menthol.** |
| 97 | Data from Japanese and Italian studies suggest that the prevalence of IQOS use is lower in never and former smokers compared to current smokers and that fewer youth than adults currently use IQOS in Japan or Italy. However, given that IQOS is still a relatively new product, the extent to which youth will initiate and use IQOS is unknown. Nevertheless, current evidence indicates IQOS uptake by youth and nonsmokers will be low. Further, limited flavor choices may reduce IQOS’ appeal to youth.Notes that the social science reviewers concerned that data regarding IQOS use in youth are limited; however, TPL says “it could be difficult and impracticable to obtain data that would satisfy the reviewers’ concerns in a pre-marketing environment.” |
| 97 | Actual use and WOT studies evaluated likelihood of current cigarettes smokers switching to IQOS. Data from these studies suggest that most smokers become dual users or at least go through a dual use phase before quitting.Less than 10% of cigarette smokers in the US actual use study switched to exclusive IQO use during the study; however, the proportion of exclusive IQOS users remained steady during the 6-week observational period, suggesting that individuals who initiate IQOS and use it for at least 95% of their tobacco intake are able to maintain exclusive IQOS use over time, and potentially replace their use of CC with IQOS long-term.The toxicological and clinical studies did not demonstrate an increase in HPHCs for dual users, and some HPHC exposures decreased (although not statistically significant). |
| 97-98 | Population Health Impact Model – applicant concluded that introducing IQOS in US would lead to a sizeable public health benefit in terms of reduced cigarette smoking and tobacco-related mortality. However, limitation to the modeling assumption, including only considered cigarettes and IQOS (not e-cigs or other tobacco products), population size does not change over time, no justification for the assumption that nonsmokers will not use IQOS, and 20-year projections is relatively short for evaluating long-term health effects. Concludes that “the overall analysis of the population model does not provide evidence to support the application.” |
| 98 | Sample labeling materials did not raise concerns. Section was redacted, but from context seems that PMI will provide “additional sport along with the instructions” included in the IQOS device to resolve issues related to product use and consumer understanding. |
| 98-99 | **A. Recommendation for marketing** |
|  | TPL recommends PMTAs be authorized subject to changes in proposed product labeling and advertising for IQOS:* Include warning: “WARNING: This product contains nicotine. Nicotine is an addictive chemical.”

(Warning should appear on package labels for Heatsticks and on all kits containing Heatsticks, as well as in all advertisements for such products and kits.)Because data show that consumers do not accurately perceive the addiction risks of IQOS, permitting IQOS to be marketed without this warning would not be appropriate for protection of public health.* Removal of warning: “SURGEON GENERAL’S WARNING: Cigarette Smoke Contains Carbon Monoxide.”

Warning is misleading with these products which, although categorized as cigarettes, do not produce CO above environmental levels and do not increase CO-related health risks. |
| 98-99 | TPL states that none of the statutory grounds for denial of a PMTA application under TCA section 910(c)(2) apply. Specifically:1. **Permitting the marketing of IQOS is appropriate for the protection of the public health, subject to the labeling and advertising changes recommended;**
2. The methods and facilities used for the manufacture, processing, and packing of IQOS conform with statutory requirements;
3. **The labeling (when changed as recommended) is not false or misleading in any particular;** and
4. The products do not fail to conform to any tobacco product standards under section 907.

**The application and FDA’s analysis does not support these conclusions.** The application did not adequately consider or provide sufficient evidence concerning:* dual use;
* use by former and never smokers, including youth;
* whether IQOS will become popular with youth and young adults;
* whether consumers understand what it means to “switch completely,” let alone whether they will switch completely;
* whether any purported benefits would be realized by dual users;
* implications of exposure to many HPHCs;
* whether reduction in exposure to some HPHCs would result in reduced health risks, or have long-term health benefits;
* population model had many limitations, including not considering many possible health impacts, and not considering long-term use;
* whether chip technology (i.e., the ability for PM to monitor use and remotely control the device) will maximize addiction potential and abuse liability;
* whether marketing plans will entice former or never smokers, including youth, to initiate with IQOS;
* because the labeling, especially reduced exposure claims, are likely to be misunderstood, especially by youth, they are false or misleading;
* the proposed addition of the “nicotine is addictive” warning will not eliminate the potential for users to misunderstand the health implications of IQOS;
* insufficient justification was provided for removing the CO warning; in any case, the removal of that warning would not improve public health outcomes;
* TPL did not appropriately apply the public health standard, requiring FDA to consider the likelihood that non-users will begin using the product, and the likelihood that current users will quit. Rather, it seemed to only compare whether IQOS use would be no worse than conventional cigarette use;
* The analysis did not compare IQOS to other tobacco products. For example, it did not consider whether IQOS may have worse health risks than e-cigarettes.
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| 99-110 | **Post-marketing recommendations, recordkeeping, retention, reporting and marketing requirements.** |
| 100 | “FDA encourages you to consider measures to limit youth-exposure to any of the products’ labeling, advertising, marketing, and/or promotion appearing in print media publications.”FDA is just “encouraging” marketing that is not seen by kids, but not *requiring* this. |
| 107 | The order requires:Inclusion of the warning statement” WARNING: This product contains nicotine. Nicotine is an addictive chemical.” on the package labels of all HeatSticks packs and of all kits containing HeatSticks packs as well as in all advertisements for such products and kits. Specifically, the warning statement must appear directly on the package and must be clearly visible underneath any cellophane or other clear wrapping [with certain specifications].” The warning statement is not required on the IQOS device, which is often sold separately.  It should also be on the device, replacing the statement, “This product contains nicotine” with “The only use for this product is to consume nicotine.” |
| 109 | The order also includes specific requirements regarding targeting delivery of and first- and/or second-party age-verified data for “labeling, advertising, marketing, and/or promotion appearing in **paid digital media** (e.g., paid digital banner advertisements for the product(s) running on another company’s website; paid advertising for the products) running in social media; paid distribution of influencer content) – whether conducted by you, on your behalf, or at your direction…” [emphasis in the original]The Reuters story showed that they are not doing this.Kirkham C, Reuters, Exclusive: Philip Morris suspends social media campaign after Reuters exposes young ‘influencers.’ May 10, 2019. Available at: <https://www.reuters.com/article/us-philipmorris-ecigs-instagram-exclusiv/exclusive-philip-morris-suspends-social-media-campaign-after-reuters-exposes-young-influencers-idUSKCN1SH02K>Statement of Matthew L. Myers, Campaign for Tobacco-Free Kids, May 10, 2019. Philip Morris Caught Re-Handed Marketing IQOS to Young People on Social Media. May 10, 2019. Available at: <https://www.tobaccofreekids.org/press-releases/2019_05_10_pmi_iqos_socialmedia_marketing>Campaign for Tobacco-Free Kids, IQOS Social Media Examples. <https://www.tobaccofreekids.org/media/2019/iqos-marketing> |
| 111-122 | **Appendix: The Public Health Rationale for Recommended Restrictions on New Tobacco Product Labeling, Advertising, Marketing, and Promotion** |