

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
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Comment regarding: Modified Risk Tobacco Product Applications: Applications for IQOS system with Marlboro Heatsticks, IQOS system with Marlboro Smooth Menthol Heatsticks, and IQOS system with Marlboro Fresh Menthol Heatsticks Submitted by Philip Morris Products S.A (“PMI”) [[link](#)]

Docket: [FDA-2017-D-3001](#)

Federal register: [82 FR 27487](#) 15 June 2017

Comment date: 12 December 2017

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Summary of comment

1. FDA has announced a comprehensive nicotine strategy that involves reducing nicotine in cigarettes to non-addictive (i.e. non-rewarding) levels. For such a strategy not to fail, it is important that the 38 million smokers in the United States have satisfactory alternatives. Many millions will want or need access to reduced risk tobacco and nicotine alternatives to cigarettes – i.e. nicotine products that do not involve combustion and are at the low end of the spectrum of risk in nicotine products.
2. It is important that such products are available and appeal to smokers in sufficient numbers to avoid widespread rejection of the comprehensive nicotine strategy. That means that smokers must have a good understanding of one of the most important features of such products – that they are much less risky. Public and professional understanding of the “the continuum of risk” and the significant discontinuity in risk between combustible and noncombustible products is very poor and deteriorating. FDA-regulated MRTP claims could partly address this deficit in understanding.
3. The MRTP claims proposed by Philip Morris International are reasonable, easily understood and embedded in wider statements of the evidence coupled with appropriate warning information. The existing statutory warnings for cigarettes are not appropriate for these products because they do not have the same risk characteristics as cigarettes. The “PMI important warnings” proposed by PMI are appropriate and proportionate.
4. The evidence provided by the applicant is comprehensive, well-executed and compelling. The evidence is grounded in the basic differences in physics and chemistry of the processes involved in IQOS and cigarettes and it consists of the toxicological profile of the IQOS vapor, studies in cell cultures and animals, clinical trials with human subjects, and behavioral assessments.
5. Given the evidence presented, it is highly unlikely that the claims as presented are false or would be misunderstood. It would take unknown and implausible mechanisms for these products *not* to be much less harmful than cigarettes. It is beyond dispute that exclusive use of IQOS as an alternative to cigarette smoking creates substantially lower exposures to harmful or potentially harmful agents.
6. We highlight data from Japan showing a dramatic decline in cigarette use driven by displacement of smoking by heated tobacco products, notably IQOS.
7. We are concerned that residual and inevitable uncertainty or the lack of multi-decadal health data will be a barrier to FDA providing consumers with important risk information that underpins their right to make informed choices about their health.
8. In response we stress the responsibility of the regulator to avoid the harms arising from *disallowing or delaying valid claims*. We urge the regulator to place equal weight on the risk of making errors in both allowing and in disallowing a claim. Both can have serious implications for health.
9. In allowing a claim, the regulator retains the power to revoke or challenge it. The applicant has to conduct post-market surveillance, allowing any problems to be identified and addressed as they arise. These regulatory tools substantially mitigate the consequences of allowing a claim in error.
10. Significant youth uptake is unlikely, given the pricing, branding and product characteristics of IQOS.

1 Strategic considerations

1.1 The importance of low-risk alternatives in FDA's new nicotine strategy

In FDA's 28 July announcements on nicotine strategy¹, the agency proposed an internally coherent approach nicotine, tobacco and health that would: (1) degrade the nicotine-based reward system of cigarette smoking; (2) improve the quality and availability of low-risk nicotine-based alternatives; (3) provide protections against nicotine initiation by adolescents; and (4) improve smoking cessation medications. The IQOS product fits well into this strategy, along with vaping products, smokeless tobacco, pharmaceutical smoking cessation treatments and new innovative products not yet visible.

Low risk alternatives such as IQOS will be integral to this strategy in the following ways ².

1. Low-risk alternatives to cigarette smoking that will meet the needs of almost all smokers as alternatives to cigarettes will need to be in place. Without such alternatives, the policy of reducing nicotine would be an excessively coercive intervention in the personal behaviors of 38 million American smokers and likely to fail for practical, political or legal reasons. That the IQOS system is much lower risk than smoking with strong appeal to smokers is discussed in [section 2](#).
2. A *wide range* of alternatives is required. Reliance on a narrow range of technology options (NRT or vaping) would potentially exclude smokers with a strong preference for tobacco flavors, or other features IQOS offers people who smoke, from switching to a low risk product – and lead to unintended consequences, such as seeking out black market cigarettes or adding nicotine liquid to low nicotine cigarettes. IQOS and other heated tobacco products may reach smokers who would be unsatisfied by vaping or medical products. The success of IQOS in displacing smoking in Japan provides useful lessons in regulation and in the potential of heated tobacco products. The experience of IQOS in markets outside the United States is discussed in [section 3](#).
3. The alternatives will need to be strongly appealing to American smokers as they will be in competition with black market or internationally traded cigarettes. Key elements of the appeal of low-risk products, such as reduced exposures and relative health risk will need to be fully understood by consumers and supported by FDA actions. Excessive caution about describing risk reduction will simply increase the uptake of black market cigarettes, or delay the arrival of a politically acceptable time to start to deal with nicotine delivery of cigarettes. Excessive caution about alternatives to smoking is not cautious, but reckless and protective of the cigarette market, whether legitimate or criminal. The approach to considering risks, uncertainties and unintended consequences in making these MRTP determinations is discussed in [section 4](#).
4. It is unlikely that IQOS will create new concerns about attracting youth, given the pricing, branding and product characteristics of the product. This is discussed briefly in [section 5](#).

¹ FDA. FDA's New Plan for Tobacco and Nicotine Regulation. 28 July 2017 [\[link\]](#)

² These elements are necessary but not sufficient to underpin FDA's strategy. A full discussion of the new strategy is outside the scope of this comment.

1.2 The IQOS MRTP application

The applicant, Philip Morris International (PMI), has applied for the following three MRTP claims³.

Figure 1: Applicant's proposed claims – in summary

1. Switching completely from cigarettes to the IQOS system can reduce the risks of tobacco-related diseases.
2. Switching completely to IQOS presents less risk of harm than continuing to smoke cigarettes.
3. Switching completely from cigarettes to the IQOS system significantly reduces your body's exposure to harmful and potentially harmful chemicals.

Each claim is embedded in a statement of the “Available Evidence to Date” and accompanied by “Important Warnings” that explain the limitations of the claim – these are set out more fully below.

Figure 2: Detailed form of proposed claims and warnings

Claim #1:
AVAILABLE EVIDENCE TO DATE: <ul style="list-style-type: none">• The <i>IQOS</i> system heats tobacco but does not burn it.• This significantly reduces the production of harmful and potentially harmful chemicals.• Scientific studies have shown that switching completely from cigarettes to the <i>IQOS</i> system can reduce the risks of tobacco-related diseases.
PMI IMPORTANT WARNING: <ul style="list-style-type: none">• Reduced risk does not mean no risk. The best way to reduce your risk of tobacco-related diseases is to completely quit tobacco use.• <i>HeatSticks</i> contain nicotine, which is addictive.• Using the <i>IQOS</i> system can harm your health.

Claim #2:
AVAILABLE EVIDENCE TO DATE: <ul style="list-style-type: none">• The IQOS system heats tobacco but does not burn it.• This significantly reduces the production of harmful and potentially harmful chemicals.• Switching completely to IQOS presents less risk of harm than continuing to smoke cigarettes.
PMI IMPORTANT WARNING: <ul style="list-style-type: none">• Less risk of harm does not mean no risk of harm. The best way to reduce your risk of tobacco-related diseases is to completely quit tobacco use.• <i>HeatSticks</i> contain nicotine, which is addictive.

³ Philip Morris Products S.A. Modified Risk Tobacco Product (MRTP) Applications [\[link\]](#) The first two applications are made under §911(g)(1) (risk modification) and the third under §911(g)(2) (exposure modification) of the Tobacco Control Act [\[link\]](#)

Claim #3:
AVAILABLE EVIDENCE TO DATE: <ul style="list-style-type: none"> • The <i>IQOS</i> system heats tobacco but does not burn it. • This significantly reduces the production of harmful and potentially harmful chemicals. • Scientific studies have shown that switching completely from cigarettes to the <i>IQOS</i> system significantly reduces your body’s exposure to harmful or potentially harmful chemicals.
PMI IMPORTANT WARNING: <ul style="list-style-type: none"> • It has not been demonstrated that switching to the <i>IQOS</i> system reduces the risk of developing tobacco-related diseases compared to smoking cigarettes. • <i>HeatSticks</i> contain nicotine, which is addictive. • Using the <i>IQOS</i> system can harm your health.

The PMI *important warnings* are intended to replace the default warnings that would be applied in the absence of the MRTP because the HeatSticks meet the definition of ‘cigarette’ in the relevant law⁴ and would therefore have the default warnings associated with cigarettes as follows:

Figure 3: Existing mandatory warnings on cigarette packets

Surgeon General’s warning	New warnings (not so far implemented)
<ul style="list-style-type: none"> • Smoking Causes Lung Cancer, Heart Disease, Emphysema, And May Complicate Pregnancy. • Quitting Smoking Now Greatly Reduces Serious Risks to Your Health. • Smoking By Pregnant Women May Result in Fetal Injury, Premature Birth, And Low Birth Weight. • Cigarette Smoke Contains Carbon Monoxide. 	<ul style="list-style-type: none"> • WARNING: Cigarettes are addictive. • WARNING: Tobacco smoke can harm your children. • WARNING: Cigarettes cause fatal lung disease. • WARNING: Cigarettes cause cancer. • WARNING: Cigarettes cause strokes and heart disease. • WARNING: Smoking during pregnancy can harm your baby. • WARNING: Smoking can kill you. • WARNING: Tobacco smoke causes fatal lung disease in nonsmokers. • WARNING: Quitting smoking now greatly reduces serious risks to your health.

These existing warnings are self-evidently inappropriate to apply to the IQOS products because they refer to cigarettes, not a non-combustible tobacco product. In terms of health impacts, the IQOS HeatSticks are not cigarettes, not smoked, and do not produce the products of combustion which are

⁴ Federal Cigarette Labeling and Advertising Act (15 U.S.C. 1333) [\[link\]](#). In 15 U.S.C 1332 The term "cigarette" means- (A) any roll of tobacco wrapped in paper or in any substance not containing tobacco. The warnings detailed in this Act have yet to be implemented, and the warnings on packs continue to be the Surgeon General warnings.

the primary causes of disease and other harms listed in these warnings. It is essential that relevant warnings are used – these statutory default warnings are not applicable, and no evidence exists to support their use. They would be misleading and damaging.

We argue that, beyond reasonable doubt, the IQOS and Heatstick products under evaluation create substantially reduced toxic exposures to users than cigarette smoking, and that implausible and unknown mechanisms would be required for this substantial reduction in exposure *not* to translate into less risk of harm or reduced risks of tobacco-related diseases. Accordingly, we think that the three claims should be accepted as framed and tested by the applicant and the relevant orders made as soon as possible. A lengthy delay in deciding the application simply means more smoking, disease and death while smokers wait to have access to and proper information about a low-risk alternative to smoking.

Do the statements convey the magnitude of risk reduction? Our main concern is that the claims requested are too weak given the likely magnitude of exposure and risk reduction. For example, the phrase “presents less risk” could be understood as 5% less, 30% less, 70% less, or 90% less – and only the last of these is likely to be approximately correct. If consumers misperceive the extent of risk-reduction, then the result is likely to be more smoking than there otherwise would be.

2 Health impacts and relative risk of IQOS

We consider that the IQOS product is a reduced-risk tobacco product creating exposures substantially lower than equivalent cigarette smoking. The magnitude of reduction in exposures and results of cell studies and human clinical trials justifies a conclusion, again, that the product will create substantially reduced risk and harm in users who switch from cigarette smoking.

The basis for this is the extensive science base developed by the manufacturer and published in high quality peer-reviewed journals specializing in regulatory science. We consider the case rests on four main strands:

1. The physical and chemical processes involved are completely different to smoking.
2. The toxicity of the IQOS aerosol is far less than cigarette smoke.
3. Biomarkers of toxin exposure are substantially and rapidly reduced after switching from smoking to heated tobacco use.
4. Reduced exposure is expected to be translated to reduced harm and disease risk

2.1 The physical and chemical process involved are completely different

Heated tobacco products have an inherently different design to cigarettes and operate at much lower temperatures. According to data from the manufacturer, the heated product design allows for electrical heating of the tobacco stick to reach a maximum temperature of 350°C (660°F). This compares to the

high combustion temperature of tobacco cigarettes, reaching up to 900°C (1650 °F) during a puff,⁵ that create the mixture of solid and liquid particles and toxic gases. The lower temperature range is specifically designed to avoid combustion and the resulting toxic emissions. Several of the most harmful toxic chemicals in smoke are products of combustion,^{6,7,8} therefore, avoiding the combustion processes is expected to reduce the toxicity of the aerosol.

2.2 The chemical profile and toxicity of IQOS aerosol is different from cigarette smoke

Evidence published from the manufacturer has clearly shown that the potentially toxic emissions from IQOS are substantially lower compared to tobacco cigarettes.

Schaller et al⁹ evaluated IQOS aerosol for the presence of 59 compounds, including 54 priority toxicants in tobacco smoke that have been listed by authorities such as the World Health Organization, the U.S. Food and Drug Administration and Health Canada (Harmful and Potentially Harmful Chemicals – HPHCs).⁸ Different puffing regimes were tested, including ISO regime, Health Canada Intense regime and more intense puffing conditions, up to 110 mL puff volume and 4.5 seconds puff duration. Substantial reductions in toxic emissions, ranging from 60-99% for different compounds, compared to a standardized tobacco cigarette (3R4F) was observed.

Similar differences were observed recently in another study by the manufacturer comparing IQOS with commercial tobacco cigarettes.¹⁰ Additionally, cytotoxicity and mutagenicity studies identified an 85-95% reduction in the potencies of IQOS compared to 3R4F cigarettes. The levels of nicotine emitted to the aerosol of IQOS were approximately 30% lower compared to 3R4F cigarettes using Health Canada Intense puffing regime. The latter finding was recently verified in an independent study comparing IQOS with commercially-available tobacco cigarettes.¹¹ Additionally, it was found that the unused tobacco stick of IQOS contains similar concentration of nicotine as the tobacco of regular cigarettes, suggesting that nicotine is not added to the tobacco stick.

⁵ Baker RR. Smoke generation inside a burning cigarette: modifying combustion to develop cigarettes that may be less hazardous to health. *Prog. Energy Combust. Sci.* 2006;32:373-385. [\[link\]](#)

⁶ U.S.DHSS. How Tobacco Smoke Causes Disease The Biology and Behavioral Basis for Smoking-Attributable Disease A Report of the Surgeon General. Public Health. U.S. Dept. of Health and Human Services, Public Health Service, Office of the Surgeon General; 2010. 792 p. [\[link\]](#)

⁷ White JL, Conner BT, Perfetti TA, Bombick BR, Avalos JT, Fowler KW, et al. Effect of pyrolysis temperature on the mutagenicity smoke condensate of tobacco. *Food Chem Toxicol.* 2001;39:499–505. [\[link\]](#)

⁸ McGrath TE, Wooten JB, Geoffrey Chan W, Hajaligol MR. Formation of polycyclic aromatic hydrocarbons from tobacco: The link between low temperature residual solid (char) and PAH formation. *Food Chem Toxicol.* 2007 Jun;45(6):1039–50. [\[link\]](#)

⁹ Schaller J-P, Keller D, Poget L, Pratte P, Kaelin E, McHugh D, et al. Evaluation of the Tobacco Heating System 2.2. Part 2: Chemical composition, genotoxicity, cytotoxicity, and physical properties of the aerosol. *Regul Toxicol Pharmacol.* 2016 Nov 30;81 Suppl 2:S27–47. [\[link\]](#)

¹⁰ Jaccard G, Tabin Djoko D, Moennikes O, Jeannet C, Kondylis A, Belushkin M. Comparative assessment of HPHC yields in the Tobacco Heating System THS2.2 and commercial cigarettes. *Regul Toxicol Pharmacol.* 2017 Aug 14;90:1-8. [\[link\]](#)

¹¹ Farsalinos KE, Yannovits N, Sarri T, Voudris V, Poulas K. Nicotine delivery to the aerosol of a heat-not-burn tobacco product: comparison with a tobacco cigarette and e-cigarettes. *Nicotine Tob Res.* 2017 Jun 16. [\[link\]](#)

Independent data on toxic emissions from IQOS were recently presented at the 48th World Conference on Lung Health.¹² A study analyzing aldehyde emissions from IQOS in comparison with tobacco cigarettes and e-cigarettes found that IQOS emits substantially lower levels of formaldehyde, acetaldehyde and acrolein compared to tobacco cigarettes, but higher levels compared to e-cigarettes. It should be noted that the levels of aldehyde emissions from IQOS found in this study were very similar to the levels reported by the manufacturer. An overall 85-90% reduction in exposure to toxic aldehydes was found when 20 IQOS HeatSticks were compared with 20 tobacco cigarettes. Of note, the study was funded by the Mayo Clinic and had no financial or other support by any commercial entity. The findings from evaluating the chemical profile of IQOS aerosol, combined with in vitro toxicity and in vivo animal effects¹³ provide evidence of a substantially lower risk associated with IQOS use compared to smoking.

2.3 The markers of toxic exposure measured in users are much lower

The manufacturer of IQOS has performed clinical studies evaluating biomarkers of exposure before and after switching from tobacco cigarettes to IQOS use. A randomized, open-label, three-arm parallel group, single-center, 5-day clinical confinement study in Poland identified a 56-96% reduction in biomarkers of toxin exposure after switching from combustible cigarettes to IQOS.¹⁴ The level of reduction was similar to smoking abstinence for many biomarkers. Similar observations were reported in another clinical confinement study in Poland¹⁵ and in a study in Japanese smokers.¹⁶ A further study undertaken in the United States is included in the application but not yet published¹⁷. Again this shows many exposure markers in IQOS users approximating to those found under smoking abstinence over the 90 day trial. The results are shown in compelling graphic form in the application Executive Summary¹⁸. The evidence clearly shows a rapid and substantial decline in biomarkers of toxin exposure when switching from smoking to IQOS use.

¹² Farsalinos K. Heat-not-burn products: benefits and risks The 48th Union World Conference on Lung Health, Guadalajara-Mexico. [\[link\]](#)

¹³ Phillips B, Veljkovic E, Boué S, *et al.* An 8-Month Systems Toxicology Inhalation/Cessation Study in Apoe^{-/-} Mice to Investigate Cardiovascular and Respiratory Exposure Effects of a Candidate Modified Risk Tobacco Product, THS 2.2, Compared With Conventional Cigarettes. *Toxicol Sci.* 2016;149:411-432. [\[link\]](#)

¹⁴ Lüdicke F, Haziza C, Weitkumat R, Magnette J. Evaluation of Biomarkers of Exposure in Smokers Switching to a Carbon-Heated Tobacco Product: A Controlled, Randomized, Open-Label 5-Day Exposure Study. *Nicotine Tob Res.* 2016 Jul;18(7):1606- [\[link\]](#)

¹⁵ Haziza C, de La Bourdonnaye G, Skiada D, Ancerewicz J, Baker G, Picavet P, *et al.* Evaluation of the Tobacco Heating System 2.2. Part 8: 5-Day randomized reduced exposure clinical study in Poland. *Regul Toxicol Pharmacol.* 2016 Nov 30;81 Suppl 2:S139–50. [\[link\]](#)

¹⁶ Haziza C, de La Bourdonnaye G, Merlet S, Benzimra M, Ancerewicz J, Donelli A, Baker G, Picavet P, Lüdicke F. Assessment of the reduction in levels of exposure to harmful and potentially harmful constituents in Japanese subjects using a novel tobacco heating system compared with conventional cigarettes and smoking abstinence: A randomized controlled study in confinement. *Regul Toxicol Pharmacol.* 2016 Nov;81:489-499. [\[link\]](#)

¹⁷ Lewis W. Farmer F. Reduced Exposure Study Using THS 2.2 Menthol With 5 Days in a Confinement Setting Followed by 86 Days in an Ambulatory Setting, 20 November 2013 Appendix 16: study ZRHM-REXA-08-US [\[link\]](#) ClinicalTrials.gov register NCT01989156 [\[link\]](#)

¹⁸ PMI, IQOS MRTP application, 2.7 Executive Summary, page 83. [\[link\]](#)[\[graphic extract\]](#)

2.4 Health - overall view

There are many studies available that would inform a judgement on relative risks and all draw conclusions that would be consistent with the result set out above. Most of these studies have been conducted by the manufacturers as part of their regulatory science initiatives, often prior to product availability. They are published in respected peer reviewed journals and reflect demanding standards expected by regulators.

It is our view that a genuinely neutral and objective assessment of the available data could only conclude that heated tobacco products pose substantially lower risks to health than cigarettes. The products are completely different in their basic chemistry and physics, the toxicity of the heated tobacco aerosol is much less than cigarette smoke, and exposure to harmful agents as measured in the body is much lower and approaches that found for smoking cessation.

Based on these insights *from what we do know*, we think it is impossible to conclude that the risks of heated tobacco products would be remotely similar to cigarette smoking and that it is rational and cautious to conclude as a working basis for policy-making that the risks to health are very much lower.

Regulators should not wait to act on such insights for many decades until the risks and benefits are known with complete certainty. The danger of such an approach to risk and uncertainty is that we implicitly encourage continued smoking – something that we know with great confidence to be highly dangerous.

3 Experience of IQOS in Japan

The purpose of this section is to show that it is possible for a product like IQOS to cause a rapid displacement of cigarette sales as smokers switch from cigarettes to IQOS. The experience of the introduction of IQOS (and then other heated tobacco products) in Japan has led to an extremely rapid decline in cigarette sales. While it cannot be assumed that IQOS would have similar impact in the United States, it does show that such a result cannot be excluded and therefore that there may be public health harms associated with refusal or delays in authorizing the product to enter the U.S. market or denying a modified risk claim that would encourage smokers to switch.

3.1 IQOS in Japan

Japan was the introductory market of the IQOS product, and the results to date appear nothing sort of extraordinary. The PMI second quarter 2017 earnings release¹⁹ gives specific information, and the key data on Japan is found in a table on page 20.

HeatSticks (IQOS) went from 2.2% of the total Japanese market in the 2nd quarter of 2016, to 10% just a year later. Combustible cigarette sales fell as smokers switched to IQOS, with IQOS already outselling Marlboro.

¹⁹ Philip Morris International. Second quarter earnings, 2017 [\[link\]](#)

Japan Tobacco's 2017 second quarter investor presentation²⁰ corroborates the PMI data. At page 4 of their news release it shows that in the first six months of this year, domestic cigarette sales in Japan fell by 11.0% (JT slightly underperformed, with a sales decline of 11.2%). At page 8 it states that their total cigarette sales forecast for Japan for the last two quarters of 2017 has been reduced by another 3 billion cigarettes. They are now forecasting that their domestic cigarette sales decline will accelerate to 12.4%.

This statement is found at page 4 of JTI's media release:

JT cigarette sales volume decreased 11.2%. This is mainly due to cigarette industry volume contraction caused by the expansion of the tobacco vapor category and a continued diminishing market trend.

And, at page 8:

The forecast of JT cigarette sales volume is revised downwards by 3.0 billion units. This reflects cigarette industry contraction including effects of the expansion of the tobacco vapor category and the continued diminishing market trend.

Tobacco stock analysts have of course been looking at the data. Here is an excerpt from the first page of an August 2 report from Berenberg Bank²¹:

Management reduced its guidance for 2017 domestic cigarette volumes from -10% to -12.5%, which implies that H2 2017 volumes will decline by 13.6%, of which around -11% is due to yoy growth in the heated-tobacco segment, primarily the IQOS brand of PMI, with the balance caused by the decline of the overall market more than offsetting share gains for Japan Tobacco within the cigarette segment. We estimate these assumptions imply that the heated tobacco segment (mostly IQOS) averages a c15% market share in H2 2017, which implies that the segment share could be around 18% by year-end.

An August 7 report on Japan Tobacco from analyst Vivien Azer of Cowen & Company²² reiterates the dramatic decline in the Japanese cigarette market but in looking at sales trends reports that the JT estimate of 18% of the national cigarette market having transitioned to heat-not-burn products by the end of this year appears conservative. This is from the introduction of that report:

While JT had begun the year anticipating a 10% industry volume decline in Japan, the company now expects full year volumes to decline 13%. In part, this reflects a deteriorating outlook in the structural rate of decline for the overall industry, after JT reported that smoking incidence fell 110 bps, to 18.2% in 2017. As such, while cigarette volumes on a long-term basis had been falling 2-3%, the underlying rate of decline is now seen as closer to 3%. Compounding these problems, of course, is the HnB category, which continues to disrupt the combustible cigarette

²⁰ Japan Tobacco 2017 second-quarter results, 3 August 2017 [\[link\]](#) Press release [\[PDF\]](#)

²¹ Jonathan Leinster, Berenberg Bank. Japan Tobacco Inc.: Waiting for Ploom Tech. August 2, 2017.

²² Vivien Azer, Cowen & Company. Japan Tobacco: Let it Burn . . . HnB Disrupts Japan Market as JT waits for Ploom Impact, August 7, 2017.

market, as industry cigarette volumes have fallen 11.0% in 1H17 (with JT relatively holding its share, down 0.1 pt for 1H17, but up 1.2 pts in 2Q17). Given the continued momentum of iQos as well as the incremental launches of Ploom Tech and BAT's glo, JT lowered their estimated industry declines for 2017 by 300 bps as the company now expects volumes to fall 13%. Indeed, the company now expects HnB to make up 12% of the total market in 2017, and 18% at the end of the year, increasing its previous estimates of 10% and 15%, respectively. We'd note that 12% of total industry volumes for 2017 implies ~20 bn HnB sticks, and considering PM has already sold nearly 10 bn sticks in 1H17 alone, and with BAT having expanded glo into Tokyo, we believe JT's estimated HnB share will prove conservative.

This movement away from combustibles in Japan is extraordinary. Even more so when the market for non-combustion alternatives is constrained due to the inability of PMI to meet the consumer demand for IQOS, delays in rollouts of other companies' heat-not-burn products, and a ban on e-cigs and smokeless tobacco.

The rate of decline in cigarette sales is, aside from the impact of a small number of one-off huge tax increases, unprecedented in wealthy countries. Even more, it appears to be not just sustainable but accelerating. In addition, the decline in cigarette consumption associated with tax increases is to a large extent the impact of continuing smokers simply reducing daily consumption, which has less impact on health than ceasing use of cigarettes entirely. By contrast, with IQOS the impact to date in Japan is very strongly connected to smokers switching entirely to the non-combustion product.

A major UBS assessment²³ documents the consumer interest, the high interest among smokers in trying the product, the conversion rate of those who do try it, and that this is happening prior to reduced-risk messaging such as the FDA can convey:

Our analysis suggests there is further potential for the category to grow in Japan as only c.20% of respondents indicated no interest in trialling the product. Additionally, of respondents that have trialled PMI's IQOS a high c.55% indicate they have converted to regular use instead of cigarettes. More encouragingly for the longer term, users are indicating that they feel healthier – prior to that message being heavily marketed as part of a 'reduced risk' framework (which could come in the future).

3.2 IQOS in other jurisdictions

PMI has also introduced IQOS into many other national markets, albeit in limited distribution channels. While the product has been gaining market share (UBS, August 11), none of these markets currently replicate the success seen in Japan. While distribution and supply constraints might partially explain this difference, the role of regulatory constraints on the marketing of any tobacco product in these countries is also likely a significant factor in slower market penetration.

²³ Carl Walton and Nik Oliver, UBS Global Research. Philip Morris International Inc: UBS Evidence Lab – next-generation products race is heating up, August 11, 2017.

3.3 Lessons from IQOS experience outside the United States

The lessons from the experience with IQOS outside the United States, echoes what has been seen with snus in Sweden, in that those who would otherwise smoke cigarettes can be facilitated in moving down the continuum of risk by the provision of consumer acceptable alternatives to cigarettes. PMI does make limited claims about iQOS in Japan: stating that the product has no smoke, no ash, less smell, that it reduces harmful constituents by 90-95%. This at least in part is a driver of the success, both commercially and for public health, of IQOS in Japan

Japanese legislation²⁴ allows for implicit or explicit health claims but requires a self-defeating and potentially misleading disclaimer “*that clearly indicates that such statements or terms do not mean that the health impacts of these products are smaller than those of other products*”. The MRTP process should allow FDA to overcome this problem.

This is hardly surprising, given the experience of informing consumers about relative risks of a myriad of other goods and services combined with making the less hazardous alternatives readily accessible. Past FDA measures to transition a marketplace in favor of better national health has been a prime example of this. For instance, the 1938 law that gave a relative advantage to science based pharmaceutical products over the existing ‘patent medicine’ products often referred to as ‘snake oil’ led to a rapid marketplace transformation. As detailed in a history of the agency²⁵:

[b]y the early 1950s, 90 percent of the prescriptions filled by patients were for drugs that did not even exist in 1938. And with the drugs came sharp drops in suffering and death.

For the FDA moving people down the continuum of risk for nicotine products, there is not just the opportunity to cause a public health revolution like what the agency did in 1938 (or, indeed, via the 1906 pure food standards that ushered the agency into existence), but to leverage modern communication techniques and technology in order to do so far more rapidly. In this way IQOS need not be seen a product that is the answer to the harms caused by combustion-based nicotine delivery so much as the start of a process.

4 Evaluating the IQOS application in the public interest – coping with uncertainty

4.1 The imperative: the information the consumer needs to make decisions

The focus should be on consumer. The most important function of information or risk claims is to communicate modified-risk characteristics *to consumers*, with a view to assisting them in making informed choices about smoking, switching to low-risk alternatives and quitting. The information

²⁴ Government of Japan, Tobacco Business Law. Section 39 and Implementing Regulations 36-2 via Tobacco Control Laws (Campaign for Tobacco Free Kids) [\[link\]](#)

²⁵ Philip J Hilts, *Protecting America’s Health: The FDA, Business, and One Hundred Years of Regulation*, p.105 (Chapel Hill, NC: University of North Carolina Press, 2003). [\[Google Books\]](#)

provided is potentially life-saving and withholding it without adequate justification is by inference potentially life-threatening.

Decision-making should not be distorted by hostility towards the tobacco industry. Although an MRTP claim confers a marketing advantage on the tobacco company making it, the evaluation should not be conducted as if it is granting a privilege to tobacco company, but as an attempt to serve the public with the best, most actionable information about their alternative options to smoking. Traditional hostility to tobacco companies should not divert a regulator's exclusive focus on the needs of the public.

Decision-making should not be distorted by attempt to manipulate behavior. The purpose of risk communication should be to provide truthful and non-misleading information on which consumers can base decisions in their own interest. The messaging should not be contrived to mislead in order to secure a particular behavior change favored Kozlowski and Sweanor describe the implications of *not* providing reasonable risk information to consumers²⁶

Concern for the principles of individual rights, health literacy, and personal autonomy (making decisions for oneself), which are key principles of public health ethics, has been countered by utilitarian arguments for the use of misleading or limited information to protect public health overall. We argue that omitting key health relevant information for current or prospective consumers represents a kind of quarantine of health-relevant information. As with disease quarantines, the coercive effects of quarantining information on differential risks need to be justified, not merely by fears of net negative public health effects, but by convincing evidence that such measures are actually warranted, that public health overall is in imminent danger and that the danger is sufficient to override principles of individual autonomy. Omitting such health-relevant information for consumers of such products effectively blindfolds them and impairs their making informed personal choices.

The inadequacy of the MRTP process alone. The MRTP process is, at best, an incomplete means of providing information to the consumer about relative risks of tobacco products. For consumers to be properly informed, it requires a tobacco company to make an investment case showing the time, cost and probability of success are justified by the commercial value of whatever claim is ultimately agreed. The provision of consumer risk information should not rely exclusively on the commercial interests of tobacco companies – no rational public health agency would design risk communication on that basis.

4.2 The problem: public misperceptions of relative risk in tobacco and nicotine products

There are extreme distortions in the public perceptions of risk of tobacco and nicotine products. For non-combustible products, the American public has perceptions of risk relative to smoking that are radically misaligned with reality and expert opinion. These misperceptions serve as an implicit protection to the cigarette trade and constitute a threat to public health by perpetuating smoking

²⁶ Kozlowski LT, Sweanor DS. Withholding differential risk information on legal consumer nicotine/tobacco products: The public health ethics of health information quarantines. *Int J Drug Policy*. Elsevier [\[link\]](#)

among people who would otherwise quit smoking by switching to low-risk alternatives, like heated tobacco, vapor or smokeless tobacco, if they were fully aware of the risks relative to smoking.

Data on e-cigarettes and smokeless tobacco illustrate the extent of the information deficit. There are no general public risk perception data on the IQOS products as they have yet to be introduced²⁷. But the situation with vaping and smokeless tobacco products is instructive. When asked how risky vaping or smokeless tobacco is compared to cigarettes, American adults gave the following answers in 2015 in a survey by the National Cancer Institute²⁸.

Figure 4: Perceptions of relative risk - cigarettes, e-cigarettes and smokeless tobacco

Compared to smoking cigarettes, would you say that electronic cigarettes are...		Do you believe that some smokeless tobacco products, such as chewing tobacco and snuff, are less harmful than cigarettes?	
Much less harmful	5.3%	Yes	10.9%
Less harmful	20.6%	No	66.2%
Just as harmful	32.8%	Don't know	22.0%
More harmful	2.7%	Other	0.9%
Much more harmful	2.0%		
I've never heard of e-cigarettes	1.2%		
I don't know enough about these products	33.9%		

Because these products do not involve combustion, the only remotely correct answers are that e-cigarettes are “much less harmful” and “yes, smokeless tobacco products are less harmful than cigarettes”. But these are shocking results, showing a dramatic misalignment of perception and reality in a way that implicitly favors continued smoking. There is also evidence that these misperceptions are worsening over time despite constantly improving specialist knowledge. A May 2016 survey²⁹ found that “forty-seven percent of respondents said vaping was not healthier than smoking conventional cigarettes compared with 38 percent who felt that way a year ago”.

4.3 Innovation in the nicotine market

Innovation always involves uncertainty, but this should not be a reason for paralysis. It is impossible to know now with complete certainty what the ultimate health impact of products like IQOS will eventually be – regulators cannot travel fifty years forward in time to observe what has still to happen. It is possible that there will be some negative effects with long term use compared to not using any tobacco product (at least that should be a working assumption), but these are likely to be greatly offset by reduced risks from displacement of smoking. It is also possible that there will be no material health impacts, or that these will be limited to specific conditions or interactions with other risks.

²⁷ PMI presents risk perception data in its application based on interviews with survey subjects exposed to the proposed MRTP messages and warnings. It concludes: *Based on the modified risk claims and communication messages, all adult consumer groups that were tested [...] were able to understand properly the following key points regarding THS: [...] THS is perceived to have less risk than cigarettes, a similar risk to e-cigarettes and more risk than NRTs aids and quitting the use of tobacco.*

²⁸ National Cancer Institute, HINTS, FDA Survey 2015. E-cigarettes [\[link\]](#); Smokeless tobacco [\[link\]](#)

²⁹ Reuters, U.S. e-cigarette use stalls as health concerns grow: Reuters/IPSOS poll, May 2016 [\[link\]](#)

Decisions must be made on the basis of what is known. This limitation applies to anything new and regulators routinely make judgements in the face of unavoidable uncertainty rather than allow uncertainty to provoke paralysis in the face of innovation or deny consumers the benefits. To make progress it is essential to assess and communicate risk insights based on available information, not wait for final certainty. The regulator’s responsibility is to make the best judgement for public health based on what is known and how this what this tells us about likely resolution of characteristics that are not, and cannot be, observed with certainty at this time.

4.4 The problem of loss aversion and prevarication

Reserving judgement does not serve the public well. It might be argued that regulators should reserve judgement until all the evidence to determine comparative risks is available – even though this may take several decades. Reserving judgement may be justifiable as ‘scientific method’, but it does not work for public health because it means information that is *highly likely* to be true is denied to consumers pending certainty, and that carries a cost – the cost of prevarication.

Not communicating a reduced risk claim that is highly likely to be valid is in itself a form of communication – it is *misleading by omission*. Not allowing a reduced-risk claim leaves the impression that no difference in risk is accepted by the regulator, a position for which there is no supporting evidence and an abundance of confounding evidence.

Decision-making in conditions of uncertainty. The diagram below maps the underlying reality onto possible regulatory decisions. If there was complete certainty and an unambiguous test of benefit for public health, then the regulatory assessment would reflect underlying reality and all decisions would be sound. However, in real-world conditions of uncertainty it possible to make errors and these have negative consequences.

Figure 5: Errors in regulatory decision-making

		Regulatory decision	
		Not approved	Approved
Appropriate for public health?	Not appropriate	Sound decision	Type 1 error “False positive”
	Appropriate	Type 2 error “False negative”	Sound decision

Type 1 errors cause harm by allowing a claim that is unjustified. Regulators have been traditionally pre-occupied with not making active decisions that could be harmful. It is easy to see why: the

consequences of a allowing a claim that turns out to be false is obviously an error that can be attributed to a regulator. When a claim is disallowed, a regulator can claim caution, or the lack of convincing evidence provided by the applicant. At the same time the costs of disallowing a claim are less obvious – potential opportunity foregone. The emphasis on the type of error is reinforced by cautionary experience of, for example, the Thalidomide tragedy³⁰.

Type 2 errors cause harm by disallowing a claim that is justified. However, the other type of error may have equally serious consequences – harms caused by not having beneficial products or being denied valuable information about risk. For example, the claim “*Switching completely from cigarettes to the IQOS system can reduce the risks of tobacco-related diseases*” is highly likely to be true, but there may be some residual uncertainty about how it is perceived or by how much the risk is reduced. The consequence of disallowing the claim because of this uncertainty could easily cause harm to consumers if they continue to believe products are no less harmful than smoking or if consumers interpret an “FDA rejection” of a claim on grounds of uncertainty to mean that the claim is invalid.

The need to take a symmetrical approach to uncertainty. Any evaluation of these claims must be approached *symmetrically*, with consideration of the risks and benefits of allowing the claims compared with the risk and benefits of disallowing the claims.

4.5 Evaluating the MRTP claims

The relevant legislation describing evaluation criteria is TCA section 911(g)³¹, which provides two options for evaluation, depending on the nature of the modified risk claim.

- Section 911(g)(1) is for the evaluation of reduced *harm* or reduced *risk* claims.
- Section 911(g)(2) is for the evaluation of reduced *exposure* claims.

In response, the applicant has provided a substantial body of evidence covering:

- The chemical characterization of the aerosol
- *In vitro* and *in vivo* studies using cell cultures and animals
- Advanced non-clinical systems toxicology enabled employing computational methods to analyze a broad array of comprehensive molecular measurements
- Clinical studies with adult smokers to evaluate exposure
- Perception and Behavior Assessments (PBA) studies undertaken in the US

There are four main reasons why the claims should be accepted:

³⁰ For example, Hamburg M. 50 Years after Thalidomide: Why Regulation Matters. FDA blog, 7 February 2012 [\[link\]](#)

³¹ Tobacco Control Act Section 911 on Modified Risk Tobacco Applications [\[link\]](#)

1. **The evidence provided to support the claims is compelling.** Taken as a whole the evidence, as summarized in Section 2 above and at length in the applicant's case provides a compelling case to support all three modified risk claims, with an acceptable and high degree of confidence. In fact, the clear implication is that these products are likely to be one to two orders of magnitude less risky than smoking based on a straightforward reading of the data provided – the expected level of exposure, risk or harm is not close to that caused by smoking cigarettes. Put another way, it is highly unlikely that the claims would be false given the evidence presented. The risk of a Type 1 error – allowing a false or misleading claim - is very low and would require novel and implausible mechanisms to cause harm for a product with the demonstrated toxicity profile, biomarkers of exposures and *in vitro* and *in vivo* results to be no less harmful than smoking. A Type-2 error – disallowing or delaying a valid claim that would help consumers - is a much greater concern given the evidence presented. It follows that the regulator is urged to avoid the harms arising from this type of error and allow the claims.
2. **Problems can be identified and addressed in post market surveillance.** It is impossible to know with certainty in advance if problems will emerge in future, but if they do such problems can be picked up in post-market surveillance and either addressed by the manufacturer or the regulator can respond by withdrawing the MRTP order (see below). Because the physical and chemical processes in IQOS are far less complex than in a burning cigarette tip, there is a greater chance that product modifications will be able to address any emerging risk without compromising the appeal of the product to smokers. Post-market surveillance provides a further means taking a small risk of making a Type 1 error in order to avoid a much more plausible and significant Type 2 error.
3. **The decision to allow these claims is not permanent and irrevocable.** The regulator should be confident in allowing the claims, because it is possible to take corrective action if it proves necessary and justified – this limiting any impact of a Type 1 error. Should it become clear that the claims are false or misleading or the product has unanticipated risks then the MRTP order can be revoked. However, it is much harder to correct an error made that disallows a valid claim because lost opportunities are much harder to recognize within a jurisdiction because they are not visible and the potential beneficiaries do not know they are deprived of a benefit. This is why we have summarized evidence from Japan in section 3 showing that there is a huge potential to reduce smoking using IQOS and other heated tobacco products. The Japan experience should justify an assumption that this IQOS will reduce smoking unless other evidence suggests otherwise. Should such evidence emerge in the United States then the regulator can respond.
4. **The risks of denying consumers valid information is high and consequences serious.** Our major concern in this submission is the costs of prevarication or denial of valid information to consumers in error (Type 2 errors). These impositions cause harm to consumers by denying them their right to make an informed choice and deny the manufacturer a right to make true and non-misleading statements about their product. The responsibility for such an error should weigh heavily on the regulator and its advisory committee.

5 Youth uptake

IQOS is clearly aimed at adult smokers. We believe substantial youth uptake of IQOS is unlikely for a variety of reasons:

- The pricing – IQOS is an expensive product with high entry costs for the device and high costs for the consumables. If the IQOS prices in the London store were applied in the United States, the IQOS starter kit would cost \$100 at current exchange rates (£89 in London).
- There is nothing in the marketing, branding or packaging that suggests any youth appeal or targeting. The product is squarely aimed at adult smokers.
- IQOS is only available with two flavors and only with nicotine delivery, and without the means to blow clouds of vapor. It is likely that some of the features of vaping (or smoking) that appeal to younger people are simply not present in IQOS.
- IQOS and HeatSticks would be covered by retailing restrictions designed to prevent sale of cigarettes to minors.
- IQOS HeatSticks would not be as freely tradable among adolescents because the market for them would be limited to those who also owned or had ready access the expensive IQOS device.
- At present there are no informal networks selling cheap illicit IQOS.

The case that youth uptake of IQOS is likely to be marginal is strong. However, there are situations where use of IQOS by a young person would be beneficial, however unlikely. This would be the case if IQOS use was as an alternative to cigarette smoking.

ENDS

12 December 2017