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

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In its application PMI presents data that it represents as showing that IQOS produces lower levels of toxic chemicals than conventional cigarettes and lower toxicological effects in animal studies. PMI also presents data on 24 biomarkers of potential harm *in human users* derived from two of their "Reduced Exposure" studies: ZRHR-REXA-07-JP in Japan, and ZRHM-REXA-08-US in the U.S. These biomarkers include measures of inflammation, oxidative stress, cholesterol and triglycerides, blood pressure, and lung function.

These human data are the most important information in the application because they represent direct evidence on how IQOS affects people. As summarized in Table 1 (page 3 of this comment) based on details in section 6.1.4.4 of the PMI MRTP application, there is no statistically detectable difference between IQOS and conventional cigarettes for 23 of these 24 biomarkers in Americans in PMI's studies. This is indicated by the fact that 23 of the 95% confidence intervals include zero (i.e., no statistically significant difference).

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

Overall, PMI's own data supports the conclusion that IQOS is no different from conventional cigarettes in terms of effects on these biomarkers of potential harm in American people.

These results are more important than all the preclinical data (aerosol toxicity and animal studies) because they represent real people smoking the actual IQOS product.

It is also important to note that PMI did not do any of these conventional statistical tests which are routine for such scientific analysis. Rather they simply emphasize the direction of changes while ignoring the fact that these differences are within what would be expected based on simple randomness. No tobacco company would tolerate such assertions made by the FDA or other public health authorities. FDA should not tolerate it coming from a tobacco company.

The results reported in PMI's application for Japan are slightly more positive for IQOS, with 3 of 13 biomarkers showing differences from conventional cigarettes (where one would expect 1 false positive by chance). These results are not strong enough to warrant drawing a conclusion of modified risk. More important, the US results are more relevant to Americans because of potential biological differences in response between Japanese and US people.

These conclusions are based on taking PMI's results at face value. Although PMI summarized the results of the ZRHR-REXA-07-JP and XZRHM-REXA-08-US Clinical Risk Endpoint (CRE) studies in Module 6.1.4 CRE, the actual studies themselves have not yet been released. Because the FDA has not yet released these and other PMI clinical studies in Module 7, it is impossible to comment on what pro-IQOS biases may have been built into the study design.

Section 911(g)(1) of the Tobacco Control Act states that FDA may issue an order authorizing marketing of a modified risk product "*only if* … the applicant has demonstrated that the product, as it is actually used by consumers, will significantly reduce harm and the risk of tobacco-related disease to individual users." ***PMI has failed to meet this statutory requirement. FDA must deny PMI's application to market IQOS as a modified risk tobacco product because PMI's own data fails to support a modified risk claim in people who are actually using the product.***

Table 1. Summary of Philip Morris Studies of Changes in Biomarkers in IQOS users compared to Conventional Cigarette Smokers (95% confidence intervals in parenthesis)		
	Japan	US
Inflammation (6.1.4.4.2*)		
White Blood Cell Count (WBC)	-0.57 GI/L (-1.04, -0.10)	0.17 GI/L (-0.47, 0.81)
C reactive protein (CRP)	6.41% ↓ (-40.75, 37.77)	16.23% ↓ (-21.69, 42.33)
Soluble ICAM (sICAM-1)	**8.72% ↓** **(2.05, 14.94)**	**10.59% ↓** **(4.03, 16.71)**
Fibrinogen	5.42% ↓ (-1.80, 12.13)	1.63% ↓ (-6.42, 9.08)
Oxidative stress (6.1.4.4.3)		
Prostaglandin F2 alpha (8-epi-PGF2α)	**12.71% ↓** **(2.55, 21.81)**	13.46% ↓ (-1.95, 23.61)
11-DTX-B2 = 11-dehydro-thromboxane B2 (11-DTX-B2)	5.42% ↓ (-1.80, 12.13)	3.56% ↓ (-23.31, 24.57)
Cholesterol and Triglycerides (6.1.4.4.4)		
High density lipoprotein-cholesterol (HDL-C)	**4.53 mg/dL** **(1.17, 7.88)**	1.4 mg/dL (-2.3, 5.0)
Low density lipoprotein-cholesterol (LDL-C)	0.87 mg/dL (-6.55, 8.30)	-3.3 mg/dL (-12.0, 5.4)
Total cholesterol	2.00 mg/dL (-6.68, 10.67)	-4.0 mg/dL (-13.3, 5.2)
Triglycerides	-6.25 mg/dL (-21.20, 8.69)	0.9 mg/dL (-12.8, 14.6)
Apolipoprotein A1 (Apo A1)	NA	3.1 mg/dL (-4.6, 10. 7)
Apolipoprotein B (Apo B)	NA	-1.6 mg/dL (-7.24, 4.03)
Physiological measures		
Systolic blood pressure	-0.59 mmHg (-3.80, 2.62)	-0.7 mmHg (-4.5, 3.1)
Diastolic blood pressure	-0.68 mmHg (-3.04, 1.69)	0.2 mmHg (-3.7, 4.0)
Lung Function (6.1.4.4.5)		
Forced expiratory volume in 1 second (FEV_1)	1.91 %Pred (-0.14, 3.97)	0.53 % Pred (-2.09, 3.00) 0.05 L (-0.06, 0.15)
FEV_1/FVC (FVC=forced vital capacity)	NA	0.00 (-0.02, 0.02)
Mid expiratory flow (MEF 25-75) (L/s)	NA	-0.67 (-6.33, 4.99)
Diffusion capacity for lung CO (DLCO) (mL/min/mmHg)	NA	0.31 (-1.09, 1.72)
Rate constant of CO (KCO) (mmol/min/kPa/L)	NA	0.05 (-0.02, 0.12)
Total lung capacity (TLC) (L)	NA	0.09 (-0.25, 0.43)
Functional residual volume (FRV) (L)	NA	-0.09 (-0.31, 0.13)
Inspiratory capacity (IC) (L)	NA	0.21 (-0.08, 0.51)
Vital capacity (VC) (L)	NA	0.10 (0.00, 0.21)
Summary		
Number of biomarkers tested	13	24
Number significantly improved	3	1
Number expected by chance	1	1
*Section of Philip Morris International's Modified Risk Tobacco Product application. The results are either IQOS:CC or IQOS-CC; CC = conventional cigarettes **Bold** results are statistically significant differences (P<05)		