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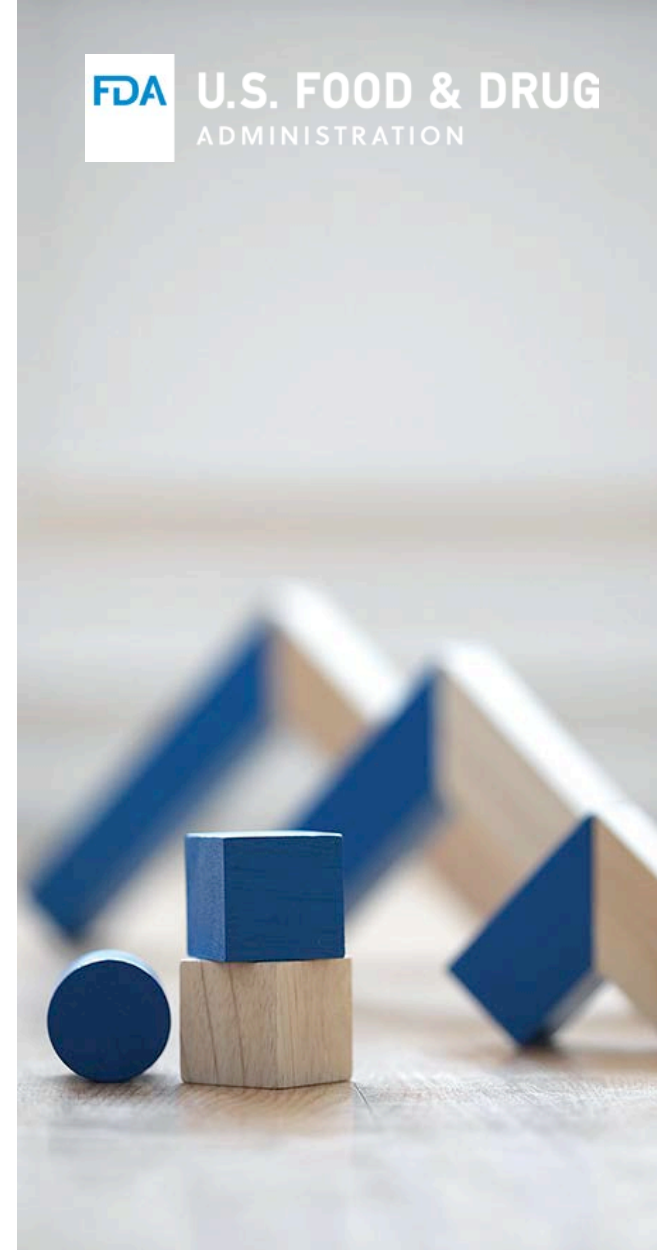
U.S. FOOD & DRUG
ADMINISTRATION

EVIDENCE RELATED TO THE HEALTH RISKS OF IQOS USE

EVALUATION OF HUMAN STUDIES

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Disclaimer: This is not a formal dissemination of information by FDA and does not represent Agency position or policy.



January 24-25, 2018

CENTER FOR TOBACCO PRODUCTS

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The applicant uses different terms to describe the products tested in the studies presented below, including the Tobacco Heating System (THS). In a March 2017 amendment to the applications, the applicant stated that THS 2.2 is the investigational product name for the product they plan to market as the *IQOS* system.

Other acronyms or abbreviations used in this presentation are:

- Atrial Fibrillation (AF)
- Biomarkers of Exposure (BOE)
- Biomarkers of Potential Harm (BOPH)
- Cardiovascular Disease (CVD)
- Chronic Obstructive Pulmonary Disease (COPD)
- Cigarettes per day (CPD)
- Combustible Cigarette (CC)
- Coronary Heart Disease (CHD)

ACRONYMS, CONTINUED

- Fagerström Test for Nicotine Dependence (FTND)
- Harmful or Potentially Harmful Constituent (HPHC)
- Low Density Lipoprotein (LDL)
- Lung Cancer (Lung CA)
- Minnesota Nicotine Withdrawal Scale (MNWS)
- Modified Cigarette Evaluation Questionnaire (MCEQ)
- Modified Risk Tobacco Product Application (MRTPA)
- Nicotine Equivalents (NEQ)
- Peripheral Artery Disease (PAD)
- Pharmacokinetic/Pharmacodynamic (PK/PD)
- Questionnaire of Smoking Urges (brief version) (QSU brief)
- Reduced Exposure (REX)

- Review of applicant's hypothesis
- Summary of human studies submitted
- Preliminary assessment of Reduced Exposure (REX) studies

APPLICANT'S HYPOTHESIS

The applicant's modified risk hypothesis can be graphically depicted as follows:



Information source: Section 2.7.1A, pages 11-12 of MRTPA's

SUMMARY OF HUMAN STUDIES



The applicant's supporting evidence included:

- Four single-use, pharmacokinetic/pharmacodynamic (PK/PD) studies
- **Four reduced exposure (REX) clinical studies**
- One actual use study
- Published clinical reports
- Perception and intention studies
- Epidemiologic studies

This presentation will focus on the REX studies with attention to Biomarkers of Exposure and Biomarkers of Potential Harm.

STUDY OVERVIEW – REDUCED EXPOSURE STUDIES



Four **Reduced Exposure (REX) Studies**

- Objective: to investigate systemic exposure to 15 HPHCs and pyrene
- Design: Randomized, controlled, open-label, ad libitum use, 3-arm parallel group (80 IQOS, 40 own-brand cigarettes, 40 smoking abstinence). Participants were ≥ 10 cpd smokers for the past month with no intent to quit. For those in the 90 day studies, subjects were requested to use assigned product exclusively during the ambulatory period.

Study ID	Location	Tobacco Flavor	# Randomized	Duration
ZRHR-REXC-03-EU	Poland	Regular	n=160	5 days confinement
ZRHR-REXC-04-JP	Japan	Regular	n=160	5 days confinement
ZRHM-REXA-07-JP	Japan	Menthol	n=160	5 days confinement, 85 days ambulatory
ZRHM-REXA-08-US	U.S.	Menthol	n=160	5 days confinement, 85 days ambulatory

Four **Reduced Exposure (REX) Studies**, continued

- Outcome Measures:
 - Biomarkers of exposure (BOE)
 - Biomarkers of potential harm (BOPH)
 - Exposure to nicotine
 - Tobacco product consumption
 - Topography
 - Subjective effects (e.g., QSU-Brief, MNWS, FTND, MCEQ)

OVERVIEW OF BIOMARKERS IN REX STUDIES

BIOMARKERS OF EXPOSURE (BOEs)



- In the REX studies, BOEs provided quantitative evidence of systemic exposure to HPHCs or their metabolites
- The applicant chose 16 BOEs for assessment based on the corresponding HPHCs or pyrene. The applicant's selection criteria were:
 - HPHCs represented both chemical and organ toxicity classes as defined by the FDA
 - HPHC reflects a specific toxic exposure or is a reliable surrogate of exposure to HPHCs
 - HPHCs cover a broad range of formation temperatures
 - HPHC is specific to cigarette smoking with other sources being minor or non-existent
 - BOE for each HPHC is reliably detectable using validated, reproducible, precise analytical methods
 - BOE for each HPHC has a half-life that is suitable for the schedule of assessments

BIOMARKERS OF EXPOSURE

Table 3 List of PMI's Selected HPHCs with their Corresponding Biomarkers of Exposure

BoExp	HPHCs	Abbreviation (BoExp)
Monohydroxybutenyl-mercapturic acid	1,3 Butadiene	MHBMA
3-Hydroxypropylmercapturic acid	Acrolein	3 HPMA
S-Phenylmercapturic acid	Benzene	S-PMA
Carboxyhemoglobin	Carbon monoxide (CO)	COHb
Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol	4 (Methylnitrosamino)-1-(3-pyridyl)-1butanone (NNK)	Total NNAL
Total 1-hydroxypyrene	Pyrene #	1-OHP
Total N-nitrosonornicotine	N-nitrosonornicotine	Total NNN
4-Aminobiphenyl	4-Aminobiphenyl	4-ABP
1-Aminonaphthalene	1-Aminonaphthalene	1-NA
2-Aminonaphthalene	2-Aminonaphthalene	2-NA
<i>o</i> -Toluidine	<i>o</i> -Toluidine	<i>o</i> -Toluidine
2-Cyanoethylmercapturic acid	Acrylonitrile	CEMA
2-Hydroxyethylmercapturic acid	Ethylene oxide	HEMA
Total 3-hydroxybenzo[a]pyrene	Benzo[a]pyrene	3-OH-B[a]P (or B[a]P)
3-Hydroxy-1-methylpropyl-mercapturic acid	Crotonaldehyde	HMPMA
S-Benzylmercapturic acid	Toluene	S-BMA

Pyrene is not listed as a HPHC by the FDA or any other health or regulatory authority, but is nevertheless listed here because its metabolite 1-OHP serves as a surrogate for PAH in general.

Source: Section 6.1.3.2, Table 3 of MRTPAs

BIOMARKERS OF POTENTIAL HARM



- Biomarkers of Potential Harm (BOPHs), called Clinical Risk Endpoints in the applications, are defined by the applicant as “a measure of a biological process, physiological system, and/or a mechanism of action that is associated with or known to contribute to smoking-related diseases.”*
- Several were measured in the ambulatory portion of the REX studies as either secondary or exploratory endpoints to determine whether reported reduced HPHC exposure from IQOS use in the clinical studies leads to biological changes that might indicate a change in long-term disease risk, particularly for cardiovascular disease, COPD, and lung cancer.

*Source: Section 3.1.4, page 26 of MRTPAs

The applications state that the clinical risk endpoints were selected based on the following criteria:

- Evidence on association with smoking
- Evidence on relationship with ≥ 1 smoking-related health outcome
- Evidence on reversibility upon smoking cessation
- Biological plausibility
- Dose-response/temporality

Source: Section 2.7, page 89 of MRTPAs

BIOMARKERS OF POTENTIAL HARM AND DISEASE MECHANISMS



Six BOPHs were singled out for particular consideration based on their relationship to pathologic mechanisms associated with tobacco-related diseases of interest:

- Endothelial Dysfunction
- Oxidative Stress
- Lipid Metabolism
- Inflammation
- Lung function
- Platelet activation

Source: Section 2.7, page 89 of MRTPAs

BIOMARKERS OF POTENTIAL HARM

<i>Biomarker of Potential Harm (BOPH)</i>	<i>Physiologic Mechanism</i>	<i>Associated Disease(s) of Interest</i>	<i>Purported Relationship to Disease(s) from Applicant monograph</i>
Soluble intercellular adhesion molecule (sICAM-1)	Endothelial Dysfunction	CVD, COPD	<ul style="list-style-type: none"> Enables leukocyte binding then sub-endothelial migration in response to inflammation Abundant in atherosclerotic plaques
8-epi-Prostaglandin F2-α (8-epi-PGF2a)	Oxidative Stress	CVD, COPD	<ul style="list-style-type: none"> A non-enzymatic free radical-catalyzed peroxidation product of arachidonic acid Since LDL oxidation leads to CHD, could show causative link between smoking and CHD
High density lipoprotein cholesterol (HDL-C)	Lipid Metabolism	CVD, COPD, Lung CA	<ul style="list-style-type: none"> May be anti-inflammatory, anti-oxidative, anti-apoptotic, and vasodilatory May inhibit platelet aggregation
White blood cell count (WBC)	Inflammation	CVD, COPD, Lung CA	<ul style="list-style-type: none"> Association between increased WBC and coronary atherosclerosis, AF and PAD appears to be independent of smoking Clear association between WBC count and COPD and an inverse association with FEV1
Forced expiratory volume in 1 second (FEV1)	Lung function	COPD	<ul style="list-style-type: none"> Reflects physiologic state of lungs/airways and severity of COPD. Drops with age, even in non-smokers
11-dehydro-thromboxane-B2 (11-DTX-B2)	Platelet activation	CVD	<ul style="list-style-type: none"> Degradation product of and surrogate marker for, Thromboxane A2, a potent activator of platelet aggregation

Source: Section 6 of MRTPAs

PRELIMINARY ASSESSMENT OF REX STUDIES

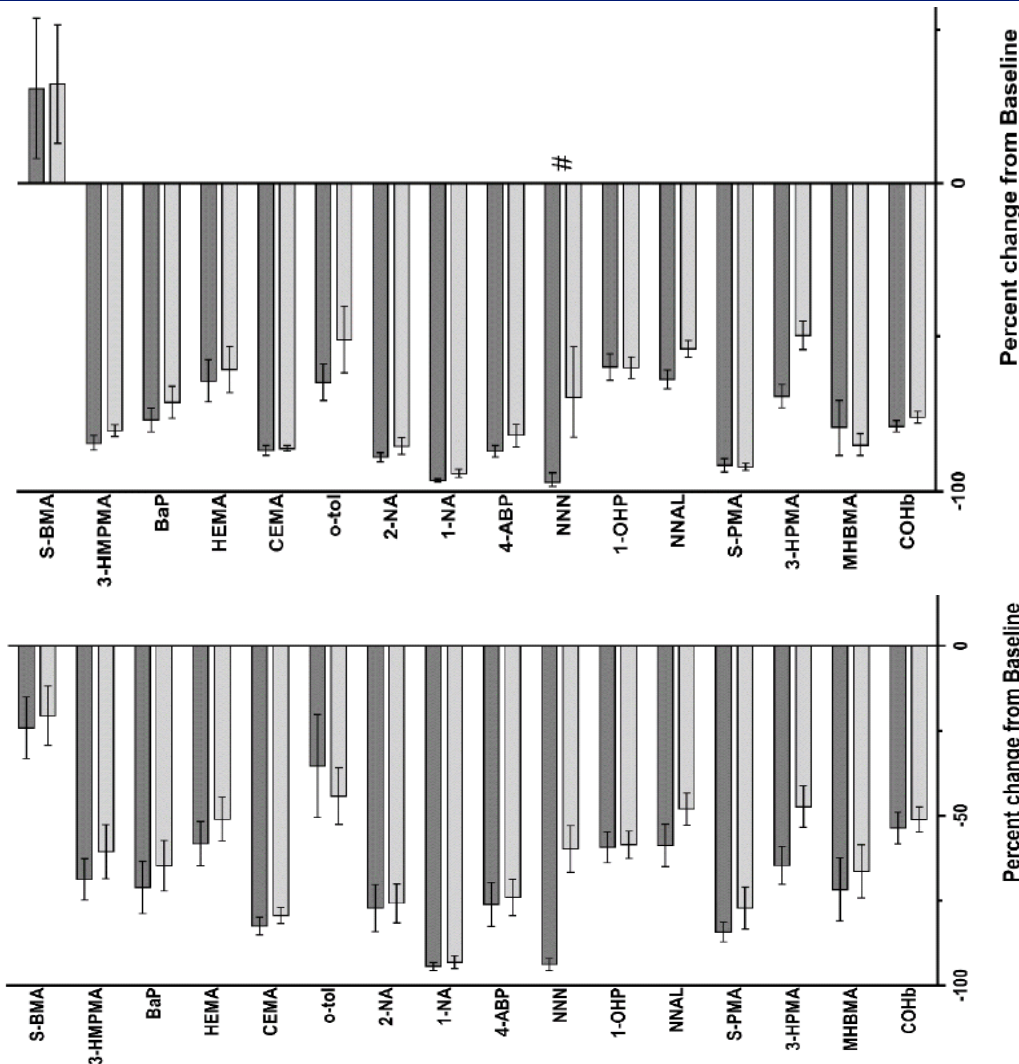
REX Studies REXC-03-EU and REXC-04-JP

The two reduced exposure studies in confinement demonstrated that switching from combusted cigarette smoking to *IQOS* (regular tobacco flavor products) resulted in a substantial reduction in systemic exposure to selected BOEs.

- Among smokers switching to *IQOS*, reductions in biomarkers were similar in magnitude to smokers in the smoking abstinence arm.
- At the end of the five-day confinement, switching from combustible cigarettes to *IQOS* use was associated with a 47 to 96% reduction* in systemic exposure to 15 of 16 selected BOEs.

*Source: Section 6.1.3.2.2.2.2.1, page 19, of MRTPAs

BOE IN 5-DAY REX STUDIES



ZRHR- REXC-03-EU

Because of one outlier in the THS arm, percent change from baseline values for total NNN are reported here as median (and Q1; Q3), both for the THS and SA arms.

Percent Change in systemic exposure to BOE from Baseline of Geometric Mean Levels and 95% CIs at Day 5

ZRHR- REXC-04-JP

■ = smoking abstinence
 □ = THS 2.2

Source: Section 6.1.3.2 of MRTPAs

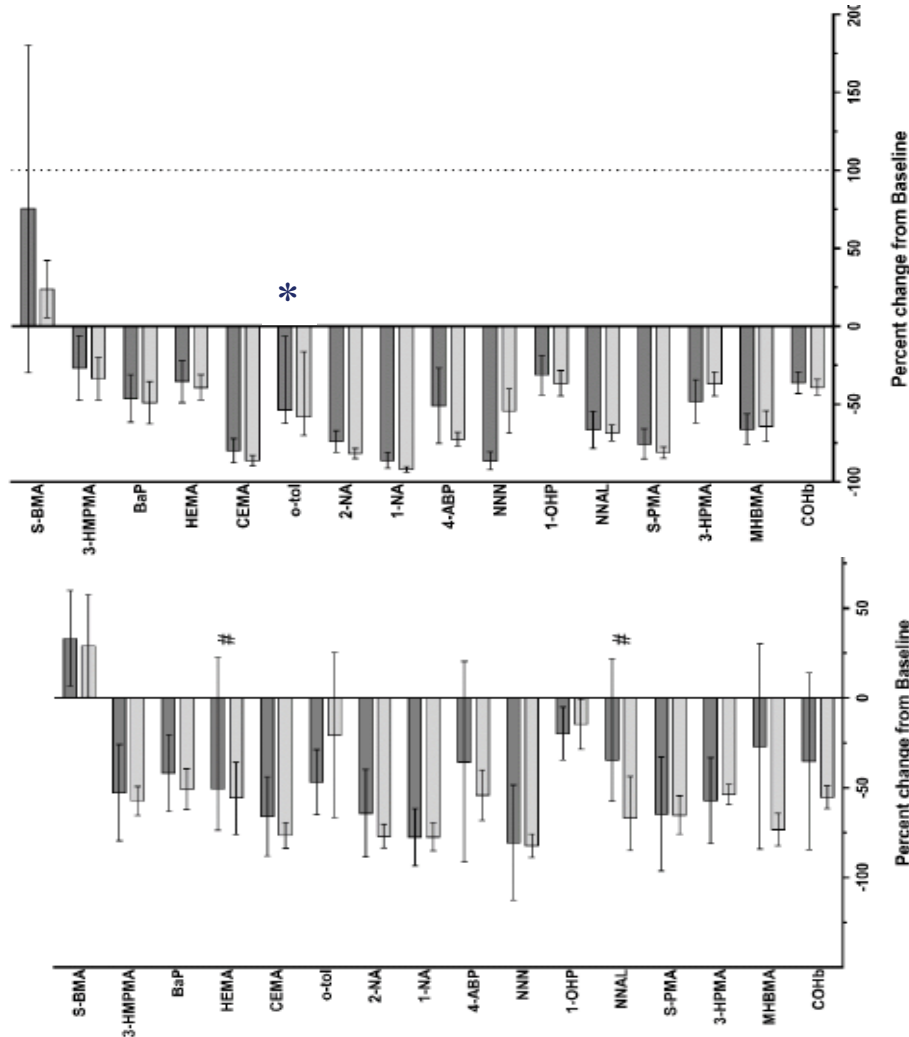
REX Studies REXA-07-JP and REXA-08-US

- At the end of the 90 day ambulatory period using mentholated products, the percentage decreases from baseline in systemic levels of 15 BOEs ranged from 34 to 92%* (REXA-07-JP) and from 15 to 82%^ (REXA-08-US). Note that these numbers exclude data for S-BMA and for NEQ.
- All decreases were statistically significant.

* Source: 6.1.3.2.2.3.2.1, Figure 5, page 25-26 of MRTPAs

^ Source: 6.1.3.2.2.3.2.1, Figure 7, page 31 of MRTPAs

BOE IN 90-DAY REX STUDIES



ZRHM-REXA-07-JP

* Because of outliers in the THS and SA arms, values percent change from Baseline values for o-toluidine are reported as median (and Q1; Q3) for both arms.

Percent Change from Baseline and 95% CIs at Day 90

ZRHM-REXA-08-US

Because of limited number of subjects in the SA arm and outliers, percent change from Baseline values for total NNAL and HEMA are reported as median (and Q1; Q3) for both for the THS and SA arms.

■ = smoking abstinence
 □ = THS 2.2

Source: Section 6.1.3.2 of MRTPAs

ANALYSES OF BOPH AT 90 DAY VISIT



Biomarker of Potential Harm	REXA-07-JP Japan		REXA-08-US United States	
WBC count	Diff THS-CC	-0.57 GI/L (-1.04, -0.10)	Diff THS-CC	0.17 GI/L (-0.47, 0.81)
sICAM-1	THS:CC % Reduction	8.72% ↓ (2.05, 14.94)	THS:CC % Reduction	10.59% ↓ (4.03, 16.71)
8-epi-PGF2α	THS:CC % Reduction	12.71% ↓ (2.55, 21.81)	THS:CC % Reduction	13.46% ↓ (-1.95, 23.61)
11-DTX-B2	THS:CC % Reduction	5.42% ↓ (-1.80, 12.13)	THS:CC % Reduction	3.56% ↓ (-23.31, 24.57)
HDL-C	Diff THS-CC	4.53 mg/dL (1.17, 7.88)	Diff THS-CC	1.4 mg/dL (-2.3, 5.0)
FEV1	Diff THS-CC	1.91 %Pred (-0.14, 3.97)	Diff THS-CC	0.53 % Pred (-2.09, 3.00)

* Data source: Section 6.1.4 of MRTPAs

Limitations of REX Studies:

- Short duration may fail to detect changes in biomarkers of potential harm that might take longer to develop
- Study results may not generalize to all U.S. smokers. Reasons may include:
 - Subjects were healthy and took no medications
 - Only one study was conducted in the United States, making genetic and cultural differences potential confounders
 - Only menthol smokers were included in the U.S. studies
 - Exposure reductions were reported among those who were adherent to study protocol, representing optimal but not necessarily real world reductions in exposure
 - Exposure profile of incomplete switchers (i.e., dual users) is unclear

Limitations of measured Biomarkers of Potential Harm:

- Analysis was secondary or exploratory and not hypothesis-based
- Biomarkers are neither tobacco specific nor disease specific
- The clinical significance of differences observed is uncertain

PRELIMINARY ASSESSMENT



Overall Preliminary Assessment:

It is not clear whether or how much the chosen biomarkers of exposure and potential harm in these reduced exposure studies are predictive of long-term tobacco-related disease risk.

CLARIFYING QUESTIONS?

