2.4 TABLE OF CONTENTS – MENTHOL 1

MODULE 1 : COVER LETTERS *

1.1 Cover Letter – THS Regular
1.2 Cover Letter – THS Menthol 1
1.3 Cover Letter – THS Menthol 2
1.4 Confidentiality Designation
1.5 TPMF Authorization Letter

MODULE 2 : TABLES OF CONTENTS, GLOSSARY, SUMMARY *

2.1 General Table of Contents
2.2 Main Table of Contents
2.3 Table of Contents – Regular
2.4 Table of Contents – Menthol 1
2.5 Table of Contents – Menthol 2
2.6 Glossary
2.7 Executive Summary

MODULE 3 : PRODUCT DESCRIPTION *

3.1 PRODUCT DESCRIPTION AND FORMULATION

3.1 Product Description and Formulation
3.1.1 General Description
3.1.2 Brand Information
3.1.3 Description of Product Components and Formulation
3.1.3.1 Tobacco Stick Regular
3.1.3.2 Tobacco Stick Menthol 1
3.1.3.3 Tobacco Stick Menthol 2
3.1.3.4 Tobacco Heating Device (THD)

* Link to Confidential Folder Index

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

3.2 DEVELOPMENT AND MANUFACTURING

3.2.1 Development – Introduction

3.2.2 Tobacco Stick Manufacturing

3.2.2.1 Manufacturing Process – Tobacco Stick

3.2.2.1.1 Manufacturing Process – Tobacco Stick Regular

3.2.2.1.2 Manufacturing Process – Tobacco Stick Menthol

3.2.2.2 Materials and Specifications

3.2.2.2.1 Tobacco Stick Regular

3.2.2.2.2 Tobacco Stick Menthol

3.2.2.3 Tobacco Sourcing, Selection and Blend

3.2.2.4 Manufacturing Control Strategy

3.2.2.5 Analytical Methods

3.2.2.6 Packaging Materials

3.2.3 Device Manufacturing

3.3 PRODUCT PERFORMANCE CHARACTERIZATION

3.3 Product Performance Characterization

3.3.1 Introduction

3.3.2 Characterization

3.3.2.1 Tobacco Stick – Regular

3.3.2.2 Tobacco Stick – Menthol 1

3.3.2.3 Tobacco Stick – Menthol 2

3.4 DESCRIPTION OF THE CONDITIONS FOR USING THE TOBACCO PRODUCT

3.4 Description of the Conditions for Using the Tobacco Product

3.5 DESCRIPTION ON HOW THE CONSUMER ACTUALLY USES THE PRODUCT

3.5 Description on how the Consumer Actually Uses the Product

MODULE 4 : LABELS, LABELING AND ADVERTISING *

4 Labels, Labeling and Advertising

A4.1.1 Brochure Reduced Risk Claim (Important Warning)

A4.1.2 Brochure Reduced Risk Claim (Statutorily-mandated warnings)

* Link to Confidential Folder Index

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

A4.1.3 Brochure Reduced Risk of Harm Claim (Important Warning)
A4.1.4 Brochure Reduced Risk of Harm Claim (Statutorily-mandated warnings)
A4.1.5 Brochure Reduced Exposure Claim (Important Warning)
A4.1.6 Brochure Reduced Exposure Claim (Statutorily-mandated warnings)
A4.1.7 Direct Mail Reduced Risk Claim (Important Warning)
A4.1.8 Direct Mail Reduced Risk Claim (Statutorily-mandated warnings)
A4.1.9 Direct Mail Reduced Risk of Harm Claim (Important Warning)
A4.1.10 Direct Mail Reduced Risk of Harm Claim (Statutorily-mandated warnings)
A4.1.11 Direct Mail Reduced Exposure Claim (Important Warning)
A4.1.12 Direct Mail Reduced Exposure Claim (Statutorily-mandated warnings)
A4.2.1 *HeatSticks* Pack – Regular – Reduced Risk Claim (Important Warning)
A4.2.2 *HeatSticks* Pack – Regular – Reduced Risk Claim (Statutorily-mandated warnings)
A4.2.3 *HeatSticks* Pack – Regular – Reduced Risk of Harm Claim (Important Warning)
A4.2.4 *HeatSticks* Pack – Regular – Reduced Risk of Harm Claim (Statutorily-mandated warnings)
A4.2.5 *HeatSticks* Pack – Regular – Reduced Exposure Claim (Important Warning)
A4.2.6 *HeatSticks* Pack – Regular – Reduced Exposure Claim (Statutorily-mandated warnings)
A4.2.7 *HeatSticks* Carton – Regular
A4.2.8 *iQOS* Printed Film – Regular
A4.2.9 *HeatSticks* Pack – Smooth Menthol – Reduced Risk Claim (Important Warning)
A4.2.10 *HeatSticks* Pack – Smooth Menthol – Reduced Risk Claim (Statutorily-mandated warnings)
A4.2.11 *HeatSticks* Pack – Smooth Menthol – Reduced Risk of Harm Claim (Important Warning)
A4.2.12 *HeatSticks* Pack - Smooth Menthol - Reduced Risk of Harm Claim (Statutorily-mandated warnings)
A4.2.13 *HeatSticks* Pack – Smooth Menthol – Reduced Exposure Claim (Important Warning)
A4.2.14 *HeatSticks* Pack – Smooth Menthol – Reduced Exposure Claim (Statutorily-mandated warnings)
A4.2.15 *HeatSticks* Carton – Smooth Menthol
A4.2.16 *iQOS* Printed Film – Smooth Menthol
A4.2.17 *HeatSticks* Pack – Fresh Menthol - Reduced Risk Claim (Important Warning)
A4.2.18 *HeatSticks* Pack – Fresh Menthol - Reduced Risk Claim (Statutorily-mandated warnings)
A4.2.19 *HeatSticks* Pack – Fresh Menthol - Reduced Risk of Harm Claim (Important Warning)
A4.2.20 *HeatSticks* Pack – Fresh Menthol - Reduced Risk of Harm Claim (Statutorily-mandated warnings)
A4.2.21 *HeatSticks* Pack – Fresh Menthol - Reduced Exposure Claim (Important Warning)
A4.2.22 *HeatSticks* Pack – Fresh Menthol – Reduced Exposure Claim (Statutorily-mandated warnings)
A4.2.23 *HeatSticks* Carton – Fresh Menthol

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

A4.2.24 *iQOS* Printed Film – Fresh Menthol
A4.2.25 *iQOS* Device Package – slate kit
A4.2.26 *iQOS* Device Package – white kit

MODULE 5 : ENVIRONMENTAL IMPACT *

5.1 Environmental Impact Assessment – THS Regular Public
A5.1.1 Environmental Impact Assessment – THS Regular Confidential
A5.1.2 Data Summaries for THS Regular
5.2 Environmental Impact Assessment – THS Menthol Public
A5.2.1 Environmental Impact Assessment – THS Menthol Confidential
A5.2.2 Data Summaries for THS Menthol

MODULE 6 : SUMMARY OF ALL RESEARCH FINDINGS *

6 SUMMARY OF ALL RESEARCH FINDINGS
6.0 Summary of All Research Findings – Index
6.1 HEALTH RISKS OF THE TOBACCO PRODUCT
6.1.1 Aerosol Chemistry and Physics
6.1.2 Pre-clinical Safety Toxicology
6.1.3.1 Justification of Selection of Biomarkers of Exposure
6.1.3.2 Summary of Biomarkers of Exposure Assessments
6.1.3.3 Bioanalytical Methods
6.1.3.4 Reduced Exposure - Overview of Studies
6.1.4 Clinical Risk Endpoints
6.1.5 Human Safety Summary
6.1.6 Conclusions on Health Risk of the Tobacco Product
6.2 EFFECT ON TOBACCO USE BEHAVIOR AMONG CURRENT TOBACCO USERS
6.2.1.1 Summary of Clinical Pharmacology Studies
6.2.1.2 PK/PD Overview of Studies
6.2.2 Product Usage Assessment among Conventional Cigarette Smokers
6.2.3 Abuse Liability Summary

* Link to Confidential Folder Index

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

6.2.4 Overall Conclusions on Use Behavior among Current Tobacco Users

6.3 EFFECT ON TOBACCO USE INITIATION AMONG NON USERS

6.3.1 Intent to Use among Tobacco Non-Users

6.3.2 Epidemiological Evidence of Tobacco Use in the US

6.3.3 Conclusions on the Effect of THS on Tobacco Use Initiation among Non-Users

6.4 EFFECT OF MARKETING ON CONSUMER UNDERSTANDING AND PERCEPTIONS

6.4 Effect of Marketing on Consumer Understanding and Perceptions

6.5 EFFECT ON THE POPULATION AS A WHOLE

6.5 Effect on the Population as a Whole

MODULE 7 : SCIENTIFIC STUDIES AND ANALYSES

7.1 PRODUCT ANALYSES

7.1 Summary of Product Characterization

7.1 Tabulated Index of Product Characterization

Droplet Size Distribution *

Report: Droplet Size Distribution – Regular

Report: Droplet Size Distribution – Menthol 1

Report: Droplet Size Distribution – Menthol 2

HPHCs: 18 in aerosol (ISO and HCI) + 6 in tobacco *

Report: Characterization of Tobacco and Tobacco Smoke – Regular

Report: Characterization of Tobacco and Tobacco Smoke – Menthol 1

Report: Characterization of Tobacco and Tobacco Smoke – Menthol 2

HPHC Comparison to Combustible Reference Products for "PMI-58" *

Report: Comparison to Combustible Reference Product 3R4F – Regular

Report: Comparison to Combustible Reference Product 3R4F – Menthol 1

Report: Comparison to Combustible Reference Product 3R4F – Menthol 2

Determination of ISO Parameters (Nicotine, CO, NFDPM) under ISO Smoking Regime *

Report: Determination of ISO Parameters Under ISO Smoking Regime – Regular

Report: Determination of ISO Parameters Under ISO Smoking Regime – Menthol 1

Report: Determination of ISO Parameters Under ISO Smoking Regime – Menthol 2

* Link to Confidential Folder Index

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

7.2 PRECLINICAL STUDIES

7.2 Summary of Pre-Clinical studies

7.2 Tabulated Index of Pre-Clinical studies

***IN VITRO* STUDIES versus Reference Product** *

Study Report: AMES Assay – Regular

Study Report: AMES Assay – Menthol

Study Report: Mouse Lymphoma Assay – Regular

Study Report: Mouse Lymphoma Assay – Menthol

Study Report: Neutral Red Uptake – Regular

Study Report: Neutral Red Uptake – Menthol

***IN VIVO* STUDIES versus Reference Product**

90 Day OECD Inhalation Study on Sprague-Dawley Rats – Regular *

Study Report: 15006 - 90 Day OECD Inhalation – THS Regular

90 Day OECD Rat Inhalation Study with Systems Toxicology Endpoints Demonstrates Reduced Exposure Effects Compared with Cigarette Smoke

90 Day OECD Inhalation Study on Sprague-Dawley Rats – Menthol *

Study Report: 15025 - 90 Day OECD Inhalation – THS Menthol

90 Day OECD Rat Inhalation Study with Systems Toxicology Endpoints Demonstrates Reduced Exposure Effects of a Mentholated Version Compared with Mentholated and Non-Mentholated Cigarette Smoke

Lung Cancer Tumorigenesis in A/J Mice in Response to Chronic Exposure *

Study Report: 15020 - Lung Cancer Tumorigenesis in A/J Mice – THS

7.3 STUDIES IN ADULT HUMAN SUBJECTS

7.3.1 CLINICAL STUDIES

7.3.1 Summary of Clinical Studies

7.3.1 Tabulated Index of Clinical Studies

01 PK01EU *

Study Report: Nicotine Pharmacokinetic Profile and Safety of the Tobacco Heating System 2.2

02 PK02JP *

Study Report: Nicotine Pharmacokinetic Profile and Safety of the Tobacco Heating System 2.2

* Link to Confidential Folder Index

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

03 REXC03EU *
Study Report: Reduced Exposure Study in Smokers Using Tobacco Heating System 2.2 with 5 Days in a Confinement Setting

04 REXC04JP *
Study Report: Reduced Exposure Study Using Tobacco Heating System 2.2 with 5 Days in a Confinement Setting

05 PK05JP *
Study Report: Nicotine Pharmacokinetic Profile and Safety of the Tobacco Heating System 2.2 Menthol

06 PK06US *
Study Report: Nicotine Pharmacokinetic Profile and Safety of the Tobacco Heating System 2.2 Menthol

07 REXA07JP *
Study Report: Reduced Exposure Study Using THS 2.2 Menthol with 5 Days in a Confinement Setting and 85 Days in an Ambulatory Setting

08 REXA08US *
Study Report: Reduced Exposure Study Using THS 2.2 Menthol with 5 Days in a Confinement Setting Followed by 86 Days in an Ambulatory Setting

Safety Update Report THS – Regular *
Safety Update Report THS – Regular

Safety Update Report THS – Menthol *
Safety Update Report THS – Menthol

Safety Update Report THS – Regular and Menthol *
Safety Update Report THS – Regular and Menthol

Safety Summary Report PBA07 – Regular and Menthol *
Report: Passive Safety Surveillance for Perception and Behavior Assessment Study – THS-PBA-07-US

THS Additional Safety Data Report – Regular and Menthol *
Report: THS Additional Safety Data

7.3.2 PERCEPTION AND BEHAVIOR ASSESSMENT (PBA) STUDIES

7.3.2 Summary of Perception and Behavior Assessment studies

7.3.2 Tabulated Index of Perception and Behavior Assessment studies

PBA01Sum *
Summary Document : PBA01 – Scales Development and Validation Project

* Link to Confidential Folder Index

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

PBA02 *
Study Report: Qualitative Study to Develop THS 2.2 Hypothetical Product Messages
PBA02 Summary: Qualitative Study to Develop THS 2.2 Hypothetical Product Messages
PBA03 *
Study Report: Study to Quantitatively Assess THS 2.2 Potential Messages
PBA03 Summary: Study to Quantitatively Assess THS 2.2 Potential Messages
PBA04 *
Study Report: Qualitative Study to Develop THS 2.2 Potential Label, Labeling and Marketing Material
PBA04 Summary: Qualitative Study to Develop THS 2.2 Potential Label, Labeling and Marketing Material
PBA05REC *
Study Report: Quantitative Assessment of THS 2.2 Label, Labeling and Marketing Material with Reduced Exposure Claims
PBA05REC Summary: Quantitative Assessment of THS 2.2 Label, Labeling and Marketing Material with Reduced Exposure Claims
PBA05RRC *
Study Report: Quantitative Assessment of THS 2.2 Label, Labeling, and Marketing Material with Reduced Risk Claims
PBA05RRC Summary: Quantitative Assessment of THS 2.2 Label, Labeling, and Marketing Material with Reduced Risk Claims
PBA05RRC2 *
Study Report: Second Quantitative Assessment of THS 2.2 Label, Labeling, and Marketing Material with Reduced Risk Claims
PBA05RRC2 Summary: Second Quantitative Assessment of THS 2.2 Label, Labeling, and Marketing Material with Reduced Risk Claims
PBA06 *
Study Report: Usability and Comprehension Study of THS 2.2 Instructions for Use Within Adult Smokers
PBA06 Summary: Usability and Comprehension Study of THS 2.2 Instructions for Use Within Adult Smokers
PBA07 *
Study Report: Actual Use Study of THS 2.2
PBA07 Summary: Actual Use Study of THS 2.2

* Link to Confidential Folder Index

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

7.3.3 Whole Offer Test studies

7.3.3 Summary of Whole Offer Test studies

7.3.3 Tabulated Index of Whole Offer Test studies

Synopsis: Whole Offer Test Study

Report: Whole Offer Test Study

7.4 POPULATION HEALTH IMPACT MODEL

7.4 Summary of Population Health Impact Model Studies

7.4 Tabulated Index of Population Health Impact Model

Simulation and Sensitivity Analysis *

Report: Simulation and Sensitivity Analysis – Population Health Impact Model

F-value Sampling

Report: Multi-variate F-factor Sampling Based on Objective Bayesian Statistics

7.5 MECHANISTIC AND SYSTEMS TOXICOLOGY (SYSTOX) STUDIES

7.5 Summary of Mechanistic and Systems Toxicology Studies

7.5 Tabulated Index of Mechanistic and Systems Toxicology Studies

***IN VITRO* STUDIES**

Systems Toxicology Assessment – Cardiovascular Disease *

Systems Toxicology-Based Assessment of the Candidate Modified Risk Tobacco Product THS2.2 for the Adhesion Of Monocytic Cells to Human Coronary Arterial Endothelial Cells

Aerosol from a Candidate Modified Risk Tobacco Product has Reduced Effects on Chemotaxis and Transendothelial Migration Compared to Combustion of Conventional Cigarettes

In vitro Systems Toxicology Assessment of a Candidate Modified Risk Tobacco Product Shows Reduced Toxicity Compared to that of a Conventional Cigarette

Organotypic Investigations *

Study Report: *In Vitro* Assessment of Acute Exposure of THS2.2 Aerosol on Organotypic Acute Human Nasal Cultures

3-D Nasal Cultures: Systems Toxicological Assessment of a Candidate Modified-Risk Tobacco Product

Study Report: *In Vitro* Assessment of the Acute Exposure of Organotypic Human Bronchial Tissue Cultures to Aerosol Produced by the Tobacco Heating System 2.2

* Link to Confidential Folder Index

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

A Systems Toxicology Approach for Comparative Assessment: Biological Impact of an Aerosol from a Candidate Modified-Risk Tobacco Product and Cigarette Smoke on Human Organotypic Bronchial Epithelial Cultures

Study Report: Assessment of the Effects of Acute Exposure of THS 2.2 Aerosol on Organotypic Human Buccal Cultures

Systems Toxicology Assessment of the Biological Impact of a Candidate Modified Risk Tobacco Product on Human Organotypic Oral Epithelial Cultures

Blood Transcriptomics *

Report: Application of Systems Pharmacology to Identify Exposure Response Markers in Peripheral Blood after Switching to a Candidate Modified-risk Tobacco Product

Application of Systems Pharmacology to Identify Exposure Response Markers in Peripheral Blood of Smokers Switching to THS2.2

Vitrocell Exposure System *

Aerosol Flow in the Vitrocell 24/48 Exposure System

***IN VIVO* STUDIES**

90-Day OECD Inhalation on Sprague-Dawley Rats – "Plus Phase" – THS Regular *

Study Report - Part 7: Summary of Results for Plus Group Animals

Study Report: Systems Toxicological Evaluation of THS2.2 90 Day Inhalation Study – OECD Plus Phase

MicroRNA Expression from a 90-Day Rat Inhalation Study Indicates that Exposure to THS 2.2 Aerosol Causes Reduced Effects on Lung Tissue Compared with Cigarette Smoke

90-Day OECD Inhalation on Sprague-Dawley Rats – "Plus Phase" – THS Menthol *

Study Report - Part 9: Summary of Results for Plus Group Animals

Study Report: Systems Toxicological Evaluation of THS2.2 90 Day Inhalation Study – OECD Plus Phase

Systems Toxicological Assessment of a Mentholated Version Revealed Reduced Cellular and Molecular Exposure Effects Compared with Mentholated and Non-Mentholated Cigarette Smoke

Studies in ApoE-deficient Mice *

Study Report: Evaluation of the Effects of THS on the Respiratory and Cardiovascular Systems of Apolipoprotein E-Deficient Mice (Parts 1 – 10) *

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

The *ApoE*$^{-/-}$ Mouse Model: A Suitable Model to Study Cigarette Smoke Induced Cardiovascular and Respiratory Diseases

* Link to Confidential Folder Index

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

Effects of Cigarette Smoke, Cessation and Switching to a Candidate Modified Risk Tobacco Product on the Liver in *ApoE*$^{-/-}$ Mice – A Systems Toxicology Analysis

Effects of Cigarette Smoke, Cessation, and Switching to Two Heat-Not-Burn Tobacco Products on Lung Lipid Metabolism in C57BL/6 and *ApoE*$^{-/-}$ Mice - An Integrative Systems Toxicology Analysis

SUPPORTING SYSTOX DOCUMENTS *

Inflammation

Lipid Biology

Oxidative Stress

Xenobiotic Metabolism

MODULE 8 : POST-MARKET SURVEILLANCE AND STUDIES *

8 Post Market Assessment Program

MODULE 9 : REFERENCES *

* Link to Confidential Folder Index

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.