APPENDIX A3.2.1-13

THS COMPARABILITY STRATEGY

THS 2.2 Comparability Strategy

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1 Introduction

Product performance comparability is a major step in the change management process. It is employed to demonstrate an absence of meaningful impact of product changes on the composition of the product aerosol and, where applicable, on the biological activity of the aerosol fractions, specifically that changes made on the product or manufacturing process do not negatively impact the performance of the product beyond the precision of the assays and the natural product variation over time. The present approach to comparability is in alignment with relevant U. S. Food and Drug Administration (FDA) and International Conference for Harmonization (ICH) guidelines. It follows a tiered approach, starting from the analytical assessment of aerosol chemistry and when necessary involving *in vitro* assays.

The selection of aerosol constituents for quantification[1] took into account priority toxicants in tobacco smoke as listed by major regulatory bodies worldwide, consitutuents with ISO-standard methods for quantification or with established biomarkers of exposure in clinical trials, potentially harmful and quantifiable constituents which are predominantly formed below 400 °C and classified by the International Agency for Research on Cancer (IARC) as Group 1 carcinogens, potentially harmful constituents which are quantifiable and predomninantly formed above 400 °C and which are classified by the IARC as Group 1 carcinogens, and several product-specific analytes such as the aerosol-former glycerin. The set of constituents selected by PMI according to these criteria is referred to as the PMI-58.

Correspondingly, the first tier of the *in vitro* assays was selected to cover different toxicity endpoints, based on their regulatory acceptance and on the feasibility of their use as an efficient screening tool. To this end, the neutral red uptake cytotoxicity, and the Ames bacterial mutagenicity or Mouse Lymphoma assays were identified as first priority.

To provide a framework for result evaluation and interpretation, B4: Withheld one page, specifications

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2 Scope

The present document summarizes statistical methods and acceptance criteria defined for THS 2.2 (Platform 1, known under its commercial name *iQOS*) product performance comparability assessments in the case of:

- Aerosol constituent yields measured at Labstat International ULC (262 Manitou Drive, Kitchener, Ontario, N2C 1L3, Canada), an independent ISO 17025 accredited tobacco testing laboratory.
- *In vitro* cytotoxicity results obtained at PMI Product Testing Laboratories, Neuchâtel, Switzerland.

3 Definitions

Long-term variability: Inherent variation in tobacco product assessment results obtained in studies conducted in the same laboratory using the same methods but at different points in time, manifested in statistically different results regardless of the number of replicates in a study[2]. Statistically, the instantaneous mean – i.e. average of measurements conducted on a single occasion, does not converge to the population mean, which can only be estimated by considering multiple measurements conducted over a long period of time. Sources for long-term variability include analytical method variance including factors such as laboratory technician or aerosol generation machine impact, product variance stemming from crop-to-crop agricultural variability, and manufacturing variability which is the study objective of a dedicated recent CORESTA Task Force.

Product performance: Chemical characterization or *in vitro* biological activity assessment of the product aerosol. Chemical characterization refers to the measurement of the yields of a number of harmful and potentially harmful constituents in the product aerosol, typically the PMI-58 list of constituents. *In vitro* biological activity refers to the assessment of *in vitro* cytotoxicity, and mutagenicity of the product aerosol. These assays were selected for their regulatory acceptance and based on their feasibility to be employed as rapid screening tools. The measure of a difference in product performance implies the evaluation of the performance of a new product variant against a reference or control product variant for each endpoint, whereby an endpoint refers to an individual aerosol constituent in the case of aerosol characterization, or an individual *in vitro* assay endpoint in the case of biological aerosol activity assessments.

Reference product: Variant of THS 2.2 which underwent pivotal pre-clinical and clinical studies. Serves as the reference point for comparability assessments.

Control product: When considering e.g. product design changes, a product configuration prior to the change being assessed. Serves as the reference point for head-to-head comparisons.

Test product: Product configuration post-change, to be compared to the reference product by means of comparability, and/or to a control product by means of a head-to-head comparison.

Comparability model: Set of statistical methods and acceptance criteria enabling comparability, initial screening, and head-to-head comparisons to be performed. Each of these three assessment types is described further in the present document.

Endpoint: a single aerosol constituent yield in the case of aerosol chemistry characterization, or an *in vitro* endpoint.

THS 2.2 monitor: A single batch of THS 2.2 (or if unavailable, different batches of the same tobacco lot set) which is analysed in parallel with study samples, with each study. The results of the THS 2.2 monitor are used during follow-up investigations to evaluate laboratory method trends over time, verify contemporary validity of tolerance estimates, and provide any further supporting evidence for an investigation.

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4.1.1 Overview

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4.1.2 (b) (4)

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(b) (4) . **Figure 1** illustrates the graphical presentation (b) (4) .

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Figure 1: illustration (b) (4)

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4.1.3 (b) (4)

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Table 1: (b) (4)

HPHC		Units	(b) (4)
Basic and product-specific endpoints	Total Particulate Matter (TPM)	mg/cig	
	Nicotine	mg/cig	
	Glycerol	mg/cig	
	Carbon monoxide (CO)	mg/cig	

Aliphatic dienes	1,3-Butadiene	(b) (4)
	Isoprene	
Carbonyls	Formaldehyde	
	Acetaldehyde	
	Acetone	
	Acrolein	
	Butyraldehyde	
	Crotonaldehyde	
	Propionaldehyde	
	Methyl ethyl ketone (MEK)	
Acid deriv.	Acetamide	
	Acrylamide	
	Acrylonitrile	
Epoxides	Ethylene oxide	
	Propylene oxide	
Nitro comp.	Nitro-benzene	
Aromatic amines	1-Aminonaphthalene	
	2-Aminonaphthalene	
	3-Aminobiphenyl	
	4-Aminobiphenyl	
	o-Toluidine	
	Benzidine	
N-heterocyclic aromatics	Pyridine	
	Quinoline	
Hal. comp.	Vinyl chloride	
Inorganic compounds	Nitric oxide (NO)	
	Nitrogen oxides (NOx)	
	Hydrogen cyanide (HCN)	

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	Ammonia (NH3)
Monocyclic aromatic hydrocarbons	Benzene
	Toluene
	Styrene
Tobacco-specific nitrosamines	N'-Nitrosoanabasine (NAB)
	N'-Nitrosoanatabine (NAT)
	N'-Nitrosonornicotine (NNN)
	4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)
Phenols	Catechol
	m-Cresol
	p-Cresol
	o-Cresol
	Hydroquinone
	Phenol
	Resorcinol
PAHs	Benzo[a]pyrene
	Benz[a]anthracene
	Dibenz[a,h]anthracene
	Pyrene
Elements	Arsenic
	Cadmium
	Chromium
	Lead
	Mercury
	Nickel
	Selenium

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4.1.6 (b) (4)

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4.2 (b) (4)

4.2.1 Overview

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4.2.2 (b) (4)

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4.2.2.1 (b) (4)

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4.2.2.2 Primary non-inferior endpoints[v]:

- Constituents classified by IARC as Group 1, 2A and 2B.
- Constituents listed by the U. S. Food and Drug Administration as constituents of cigarette smoke for which quantitative information is required.
- Constituents with associated biomarkers of exposure.
- Constituents recommended by the WHO FCTC for mandated reduction yields in smoke.

The following HPHCs from the PMI-58 list fall under this category:

Endpoint	IARC classified	FDA - 18	Biomarkers	WHO FCTC - 9
Benzo[*a*]pyrene	x	x	x	x
Formaldehyde	x	x		x
Acetaldehyde	x	x		x
Cadmium	x			
Lead	x			
Chromium	x			
Nickel	x			

[v] Non-inferiority of performance refers in this case to non-superiority of yields; for historical reasons and consistency with early reports, the terminology is maintained.

Arsenic	x			
Styrene	x			
1,3-Butadiene	x	x	x	x
Isoprene	x	x		
Acrylonitrile	x	x	x	
Benzene	x	x	x	x
NNN	x	x	x	x
NNK	x	x	x	x
Acetamide	x			
Acrylamide	x			
Ethylene oxide	x		x	
Propylene oxide	x			
Nitrobenzene	x			
o-toludine	x		x	
Vinyl chloride	x			
Benz[*a*]anthracene	x			
Dibenz[*a,h*]anthracene	x			
Ammonia		x		
1-Aminonaphthalene		x	x	
2-Aminonaphthalene		x	x	
4-Aminobiphenyl	x	x	x	
Acrolein		x	x	x
Crotonaldehyde		x	x	
Carbon monoxide		x	x	x
Toluene		x	x	
Pyrene			x	

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4.2.5 Acceptance Criteria

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6 Reference Documents

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7 Version History

Version	Date	Changes
1.0	27th March 2015	Original Document
1.1	30th March 2016	Annual review and update of head-to-head acceptance criteria.
1.1 SV	13th June 2016	Submission version – references updated to interlink within the submission