THS 2.2 Comparability Strategy

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Reviewer(s)	*See R3 workflow*	

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1 Introduction

Product performance comparability is a major step in the change management process[1]. 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[1], 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[3] took into account priority toxicants in tobacco smoke as listed by major regulatory bodies worldwide, constituents 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 constituents selected according to these criteria are 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: the neutral red uptake cytotoxicity, and the Ames bacterial mutagenicity or Mouse Lymphoma assays were identified as first priority.

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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 HEETS*) product performance comparability assessments in the case of:

- Aerosol constituent yields measured at (b) (4) [redacted], an independent ISO 17025 accredited tobacco testing laboratory.
- *In vitro* cytotoxicity results obtained at PMI Product Testing Laboratories, Neuchâtel, Switzerland and (b) (4) [redacted].

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[4]. Statistically, the 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 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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HPHC		Units
Aliphatic dienes	1,3-Butadiene	µg/cig
	Isoprene	µg/cig
Carbonyls	Formaldehyde	µg/cig
	Acetaldehyde	µg/cig
	Acetone	µg/cig
	Acrolein	µg/cig
	Butyraldehyde	µg/cig
	Crotonaldehyde	µg/cig
	Propionaldehyde	µg/cig
	Methyl ethyl ketone (MEK)	µg/cig
Acid deriv.	Acetamide	µg/cig
	Acrylamide	µg/cig
	Acrylonitrile	µg/cig
Epoxides	Ethylene oxide	µg/cig
	Propylene oxide	ng/cig
Nitro comp.	Nitro-benzene	µg/cig
Aromatic amines	1-Aminonaphthalene	ng/cig
	2-Aminonaphthalene	ng/cig
	3-Aminobiphenyl	ng/cig
	4-Aminobiphenyl	ng/cig
	o-Toluidine	ng/cig
	Benzidine	ng/cig
N-heterocyclic aromatics	Pyridine	µg/cig
	Quinoline	µg/cig
Hal. comp.	Vinyl chloride	ng/cig
Inorganic	Nitric oxide (NO)	µg/cig

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HPHC		Units	(b) (4)
compounds	Nitrogen oxides (NOx)	µg/cig	
	Hydrogen cyanide (HCN)	µg/cig	
	Ammonia (NH3)	µg/cig	
Monocyclic aromatic hydrocarbons	Benzene	µg/cig	
	Toluene	µg/cig	
	Styrene	µg/cig	
Tobacco-specific nitrosamines	N'-Nitrosoanabasine (NAB)	ng/cig	
	N'-Nitrosoanatabine (NAT)	ng/cig	
	N'-Nitrosonornicotine (NNN)	ng/cig	
	4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)	ng/cig	
Phenols	Catechol	µg/cig	
	m-Cresol	µg/cig	
	p-Cresol	µg/cig	
	o-Cresol	µg/cig	
	Hydroquinone	µg/cig	
	Phenol	µg/cig	
	Resorcinol	µg/cig	
PAHs	Benzo[a]pyrene	ng/cig	
	Benz[a]anthracene	ng/cig	
	Dibenz[a,h]anthracene	ng/cig	
	Pyrene	ng/cig	
Elements	Arsenic	ng/cig	
	Cadmium	ng/cig	
	Chromium	ng/cig	
	Lead	ng/cig	
	Mercury	ng/cig	

HPHC		Units
	Nickel	ng/cig
	Selenium	ng/cig

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4.2.1 Overview

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Endpoint	Units	Threshold	Endpoint	Units	Threshold
Hydrogen cyanide	µg/stk	17.5	Acrylonitrile	µg/stk	1.07
m-Cresol	µg/stk	0.19	p-Cresol	µg/stk	0.34

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6 Reference Documents

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7 Version History

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8 Review

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Document Information

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