APPENDIX A3.3-2

PMI-58 – LIST OF COMPOUNDS AND ANALYTICAL METHODS

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1. INTRODUCTION

The information given in the appendix are data provided by Labstat UCL, who performs analysis for PMI (see Section 3.2.2).

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2. PMI LIST OF 58 COMPOUNDS

Table 1 gives the details of the 58 compounds of interest for further characterization (refered to as the "PMI 58"), that include 54 HPHCs and four other aerosol constituants.

Table 1: PMI list of 58 Compounds (*italics: FDA's abbreviated list of 18 HPHCs*)

#	Compound	CAS	Unit	LOD	LOQ	Working Range *	Method of Analysis
1	*Carbon monoxide*	*630-08-0*	*mg/item*	*0.067*	*0.223*	*0.2 - 40*	*NDIR*
2	*Nicotine*	*54-11-5*	*mg/item*	*0.001*	*0.004*	*0.004 – 5*	*GC-FID*
3	Tar (NFDPM)	N/A	mg/item	0.071	0.237	N/A	Weighing
4	TPM	N/A	mg/item	0.060	0.200	N/A	Weighing
5	Water	7732-18-5	mg/item	0.038	0.128	0.16 – 32	GC-TCD
6	*1,3-butadiene*	*106-99-0*	*µg/item*	*0.029*	*0.095*	*0.2 - 150*	*GC-MS*
7	*Isoprene*	*78-79-5*	*µg/item*	*0.041*	*0.135*	*1 - 500*	*GC-MS*
8	*Acetaldehyde*	*75-07-0*	*µg/item*	*0.973*	*3.24*	*3 - 2000*	*HPLC-UV*
9	Acetone	67-64-1	µg/item	0.846	2.82	2 - 1200	*HPLC-UV*
10	*Acrolein*	*107-02-8*	*µg/item*	*0.713*	*2.38*	*1 - 600*	*HPLC-UV*
11	Butyraldehyde	123-72-8	µg/item	0.812	2.71	2.5 - 1700	*HPLC-UV*
12	*Crotonaldehyde*	*123-73-9*	*µg/item*	*0.988*	*3.29*	*1.5 - 800*	*HPLC-UV*
13	*Formaldehyde*	*50-00-0*	*µg/item*	*0.361*	*1.20*	*1 – 600*	*HPLC-UV*
14	MEK	78-93-3	µg/item	1.10	3.66	1 - 600	*HPLC-UV*
15	Propionaldehyde	123-38-6	µg/item	1.00	3.34	1 - 600	*HPLC-UV*
16	Acetamide	60-35-5	µg/item	0.024	0.080	0.2 - 36	GC-MS
17	Acrylamide	79-06-1	µg/item	0.061	0.203	0.2 - 20	GC-MS
18	*Acrylonitrile*	*107-13-1*	*µg/item*	*0.032*	*0.107*	*0.1 - 80*	*GC-MS*
19	Ethylene oxide	75-21-8	µg/item	0.036	0.119	0.07 - 15	GC-MS
20	Propylene oxide	75-56-9	ng/item	15.6	52.0	200 - 8000	GC-MS
21	Nitrobenzene	98-95-3	µg/item	0.011	0.038	0.02 - 2	GC-MS
22	*1-Aminonaphthalene*	*134-32-7*	*ng/item*	*0.008*	*0.027*	*0.01 - 10*	*GC-MS*
23	*2-Aminonaphthalene*	*91-59-8*	*ng/item*	*0.004*	*0.012*	*0.01 - 10*	*GC-MS*
24	3-Aminobiphenyl	2243-47-2	ng/item	0.001	0.004	0.002 - 2	*GC-MS*
25	*4-Aminobiphenyl*	*92-67-1*	*ng/item*	*0.001*	*0.005*	*0.002 - 2*	*GC-MS*
26	o-Toluidine	95-53-4	ng/item	0.010	0.034	0.04 - 40	*GC-MS*
27	Pyridine	110-86-1	µg/item	0.027	0.090	0.4 - 40	*GC-MS*
28	Quinoline	91-22-5	µg/item	0.003	0.011	0.02 - 2	*GC-MS*
29	Vinyl chloride	75-01-4	ng/item	0.657	2.19	4 – 160	GC-MS

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#	Compound	CAS	Unit	LOD	LOQ	Working Range *	Method of Analysis
30	*Ammonia*	*7664-41-7*	*µg/item*	*0.184*	*0.613*	*0.7 - 102*	*Cation exchange chromatography*
31	Hydrogen cyanide	74-90-8	µg/item	0.525	1.75	0.6 - 160	Colorimetric analyzer
32	Nitric oxides	10102-43-9	µg/item	0.171	0.569	2 - 15	Chemiluminescent emission
33	Nitrogen oxides	10102-44-0	µg/item	0.381	1.27	2 - 15	Chemiluminescent emission
34	*Benzene*	*71-43-2*	*µg/item*	*0.017*	*0.056*	*0.2 - 200*	*GC-MS*
35	Styrene	100-42-5	µg/item	0.012	0.039	0.04 - 40	GC-MS
36	*Toluene*	*108-88-3*	*µg/item*	*0.061*	*0.204*	*0.2 - 200*	*GC-MS*
37	n-Nitrosoanabasine (NAB)	1133-64-8	ng/item	0.054	0.179	0.3 - 90	HPLC-MS/MS
38	n-Nitrosoanatabine (NAT)	71267-22-6	ng/item	0.195	0.650	2 - 700	HPLC-MS/MS
39	*4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)*	*64091-91-4*	*ng/item*	*0.151*	*0.502*	*4 – 1000*	HPLC-MS/MS
40	*n-Nitrosonornicotine (NNN)*	*15443-55-8*	*ng/item*	*0.098*	*0.328*	*2 - 700*	HPLC-MS/MS
41	Catechol	120-80-9	µg/item	0.026	0.086	0.08 - 36	HPLC-Fluorescence
42	m-Cresol	108-39-4	µg/item	0.006	0.019	0.02 - 8	HPLC-Fluorescence
43	p-Cresol	106-44-5	µg/item	0.010	0.034	0.008 - 4	HPLC-Fluorescence
44	o-Cresol	95-48-7	µg/item	0.008	0.026	0.02 - 8	HPLC-Fluorescence
45	Hydroquinone	123-31-9	µg/item	0.062	0.207	0.08 - 36	HPLC-Fluorescence
46	Phenol	108-95-2	µg/item	0.026	0.086	0.08 - 36	HPLC-Fluorescence
47	Resorcinol	108-46-3	µg/item	0.016	0.055	0.02 - 8	HPLC-Fluorescence
48	*Benzo[a]pyrene*	*50-32-8*	*ng/item*	*0.106*	*0.354*	*0.16 - 2400*	*GC-MS*
49	Benz[a]anthracene	56-55-3	ng/item	0.073	0.243	0.16 - 2400	*GC-MS*
50	Dibenz[a,h]anthracene	53-70-3	ng/item	0.124	0.413	0.16 - 2400	*GC-MS*
51	Pyrene	129-00-0	ng/item	0.094	0.314	0.16 - 2400	*GC-MS*
52	Arsenic	7440-38-2	ng/item	0.360	1.20	0.06 - 1	ICP-MS-AES
53	Cadmium	7440-43-9	ng/item	0.090	0.280	0.25 - 5	ICP-MS-AES
54	Chromium	7440-47-3	ng/item	3.31	11.0	0.06 – 1.2	ICP-MS-AES

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#	Compound	CAS	Unit	LOD	LOQ	Working Range *	Method of Analysis
55	Lead	7439-92-1	ng/item	0.490	1.62	0.25 - 5	ICP-MS-AES
56	Mercury	7439-97-6	ng/item	0.209	0.695	0.5 - 15	CVAA
57	Nickel	7440-02-0	ng/item	15.9	53.1	0.25 - 5	ICP-MS-AES
58	Selenium	7782-49-2	ng/item	0.250	0.830	0.06 - 1	ICP-MS-AES

*Estimated using the typical calibration range (nominal values) multiplied by the method dilution and divided by the number of sticks used in the analysis of the "heat-not-burn" product.

3. METHODS ABSTRACT

This chapter provides the synopsis for the methods used by Labstat, whose data were used to write the study reports for the PMI 58 provided in Section 7.1.

The reference to the internal methods identification from Labstat are provided in parenthesis.

3.1. Tar, Nicotine and Carbon Monoxide (T-115/TMS-00115a)

This method is used to quantify Nicotine Free Dry Particulate Matter (NFDPM), Nicotine, CO, Water, TPM, Glycerol and Menthol

Method Synopsis

Five conditioned sticks (cigarettes) were smoked using a standard 20 port linear smoking machine equipped with a CO analyzer, onto a conditioned, pre-weighed 44mm glass fiber filter disc (pad). The gas phase was collected into a Vapour Phase (VP) collection bag and then introduced into a Non-Dispersive Infra-Red (NDIR) analyzer and the % CO determined. The pad was re-weighed with the difference calculated as the Total Particulate Matter (TPM). The pad was extracted with isopropanol (IPA) containing the internal standards (trans-anethole for nicotine and methanol for water), and the extract analyzed for nicotine and water by gas chromatography (flame ionization detector (FID) for nicotine and thermal conductivity detector (TCD) for water). The nicotine-free dry particulate matter (NFDPM; 'tar') value was determined by subtracting the water and nicotine from the TPM result.
For the analysis of "heat-not-burn" products, no additional changes to the sample generation, collection or sample preparation of the base method for cigarettes were required.

3.2. Method Modifications for the Determination of Glycerol and Menthol (TMS-00115a Appendix)

A second independent aliquot of the IPA extract is used to determine propylene glycol and menthol by gas chromatography (GC) with flame ionization detector (FID) using a megabore

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DB-Wax fused silica column that has a polyethylene glycol (PEG) stationary phase, as per Health Canada method T-304. Quantification is achieved using the internal standard calibration (internal standard: trans-anethole).

3.3. Carbonyls (T-104/TMS-00104)

This method is used to quantify Acetaldehyde, Acetone, Acrolein, Butyraldehyde, Crotonaldehyde, Formaldehyde, Methyl Ethyl Ketone and Propionaldehyde.

Method Synopsis

Two conditioned sticks (cigarettes) were smoked on a standard 20 port linear smoking machine that was fitted with Drechsel-type bottles or traps with fritted impingers. The unfiltered mainstream tobacco smoke was scrubbed of volatile carbonyls by passing each puff through an impinger into a trap containing 80mL of an acidified solution of 2,4-dinitrophenylhydrazine in acetonitrile. An aliquot of the reacted DNPH-smoke extract was then syringe-filtered and diluted with 1% trizma base in aqueous acetonitrile. The samples were subjected to reverse phase high performance liquid chromatography (HPLC) and quantified via ultra violet detection.
For the analysis of "heat-not-burn" products, no additional changes to the sample generation, collection or sample preparation of the base method for cigarettes were required.

3.4. Phenols (TMS-00139)

This method is used to quantify *o*-Cresol, *m*-Cresol, *p*-Cresol, Catechol, Resorcinol, Hydroquinone and Phenol.

Method Synopsis

Five conditioned sticks (cigarettes) were smoked per port on a standard 20 port linear smoking machine. The mainstream total particulate matter (TPM) was collected on a conditioned, pre-weighed 44mm glass fiber filter disc (pad). The pad was then extracted with 20 mL of 1% acetic acid (HOAc). An aliquot of the TPM extract was syringe filtered, diluted and subjected to reversed-phase gradient liquid chromatography. Phenols were monitored using selective fluorescence detection and quantified by comparison to an external standard calibration.

Method Modifications

For the analysis of "heat-not-burn" products, ten sticks were smoked per port on a standard 20 port linear smoking machine. An impinger containing 20mL of 1% acetic acid (HOAc) was added in the smoke train after the pad. The pad was replaced after five sticks were smoked per port for HCI smoking conditions (two pads per replicate for HCI). The collection pad for ISO smoking conditions was extracted with the impinger solution (20mL). An additional 20mL of

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1% acetic acid was added to the impinger solution to extract the two pads per replicate for HCI smoking conditions (total of 40mL per replicate).

3.5. Aromatic Amines (TMS-00128)

This method is used to quantify 1-aminonaphthalene, 2-aminonaphthalene, 3-aminobiphenyl and 4-aminobiphenyl.

Method Synopsis

Ten conditioned sticks (cigarettes) were smoked on a standard rotary smoking machine. The mainstream total particulate matter (TPM) was collected on a conditioned, pre-weighed 92mm glass fiber filter disc (pad). The pad was quartered and extracted with 100mL of 5% hydrochloric acid solution. The extraction flask was shaken for 30 minutes on a wrist-action shaker and the contents filtered into a 500mL separatory funnel. The internal standards (d5-aniline, d9-o-toluidine, d7-o-anisidine, d7-4-aminobiphenyl, d8-benzidine) were spiked into the solution. The filtrate was washed with dichloromethane, made basic with sodium hydroxide solution and extracted with hexane. The hexane extracts were dried with sodium sulphate, derivatized with pentafluoropropionic acid anhydride (PFPA) and trimethylamine, concentrated by rotary evaporation, passed through a florisil column, and quantified using gas chromatography – mass spectrometry (GC/MS) with ion trap under full scan mode.

Method Modifications

For the analysis of "heat-not-burn" products, a standard 20 port linear smoking machine and a 44mm pad was used instead of a rotary smoking machine. The 44mm pad was replaced after five sticks were smoked per port for HCI smoking conditions (two pads per replicate for HCI). Lower calibrations standards were prepared with the addition of d7-1-aminonaphthalene, d7-2-aminonaphthalene as internal standards. Quantification was achieved using negative chemical ionization (NCI) gas chromatography – mass spectrometry (GC/MS) operating in selective ion monitoring (SIM) mode.

3.6. Ammonia (T-101/TMS-00101)

Method Synopsis

Five conditioned sticks (cigarettes) were smoked on a standard rotary smoking machine. The mainstream smoke was passed through a conditioned, pre-weighed 92mm glass fiber filter disk (pad) and then into two impingers placed in series after the pad, each containing 15mL of 0.1N sulfuric acid. The pad, after being weighed to determine the mainstream total particulate matter (TPM), was extracted with the contents of the two impingers. The mixture was then filtered through a 0.45 µm syringe filter into an auto-sampler vial and analyzed by cation exchange chromatography using an external standard calibration.

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Method Modifications

For the analysis of "heat-not-burn" products, the sticks were smoked on a standard 20 port linear smoking machine using two impingers per port as smoked on a rotary machine.

3.7. Tobacco Specific Nitrosamines (TMS-00135)

This method is used to quantify Nitrosonornicotine (NNN), Nitrosoanatabine (NAT), Nitrosoanabasine (NAB) and 4-(N-nitrosomethylamino-1-(3-pyridyl)-1-butanone (NNK)

Method Synopsis

Five conditioned sticks (cigarettes) were smoked per port on a standard 20 port linear smoking machine. The mainstream total particulate matter (TPM) was collected on a conditioned, pre-weighed 44mm glass fiber filter disc (pad). The pad was spiked with a deuterium labeled internal standard solution (containing NNN-d4, NAT-d4, NAB-d4, and NNK-d4) and then extracted with a 100mM ammonium acetate solution. The extract was then filtered and subject to LC-MS/MS analysis with positive electrospray ionization (ESI). Two mass transition pairs for each analyte can be used to assist analyte confirmation and quantification. The most intense pairs are used for quantification while the less intense transition pairs are used as qualifiers for further compound confirmation.

For the analysis of "heat-not-burn" products, no additional changes to the sample generation, collection or sample preparation of the base method for cigarettes were required.

3.8. Semi Volatiles (T-112/TMS-00112 & TMS-00137)

This method is used to quantify Pyridine, Quinoline, Styrene, Nitrobenzene, Acetamide and Acrylamide.

Method Synopsis

Twenty conditioned sticks (cigarettes) were smoked on a standard rotary smoking machine. The mainstream smoke was passed through a conditioned, pre-weighed 92mm glass fiber filter disc (pad) and then into two cryogenic traps placed in series after the pad, each containing 20mL of methanol. The pad was then cut into quarters, spiked with the internal standard solution (containing d5-pyridine, d8-styrene and d7-quinoline) and extracted with the 40 mL of methanol from the two cryogenic traps. An aliquot of the extract was syringe filtered into an auto-sampler vial and analyzed using gas chromatography – mass spectrometry (GC/MS) with ion trap under full scan mode.

Method Modifications

For the analysis of "heat-not-burn" products, ten sticks were smoked per port on a standard 20 port linear smoking machine using a 44mm pad instead of a rotary smoking machine. The pad was replaced after five sticks were smoked per port for HCI smoking conditions (two pads per

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replicate for HCI). d5-acetamide and d3-acrylamide were added as internal standards and analysis was done by gas chromatography – mass spectrometry (GC/MS) using a single quadrupole mass detector operating under selective ion monitoring (SIM) mode.

3.9. Selected Volatiles (TMS-00124)

This method is used to quantify 1,3-butadiene, Isoprene, Acrylonitrile, Benzene and Toluene.

Method Synopsis

Ten conditioned sticks (cigarettes) were smoked on a standard rotary smoking machine. The mainstream smoke was passed through a conditioned, pre-weighed 92mm glass fiber filter disc (pad) and then into two cryogenic traps placed in series after the pad, each containing 10mL of methanol. An aliquot of the solution from the two traps was spiked with the internal standards (d6-benzene, d8-styrene and d5-pyridine) and analyzed by gas chromatography – mass spectrometry (GC/MS) with ion trap under full scan mode.
A second aliquot of the solution from the two traps was derivatized with 48% hydrobromic acid, then spiked with internal standards (d6-benzene and d4-2-bromoethanol) and analyzed for ethylene oxide via gas chromatography – mass spectrometry (GC/MS) operating under selective ion monitoring (SIM) mode.

Method Modifications

For the analysis of "heat-not-burn" products, ten sticks were smoked per port on a standard 20 port linear smoking machine using a 44mm pad instead of a rotary smoking machine. The pad was replaced after five sticks were smoked per port for HCI smoking conditions (two pads per replicate for HCI). Lower calibrations standards were prepared and analysis of the trapping solution was done by gas chromatography – mass spectrometry (GC/MS) using a single quadrupole mass detector operating under selective ion monitoring (SIM) mode.

3.10. Trace Metals (T-109/TMS-00109)

This method is used to quantify Arsenic, Cadmium, Chromium, Lead, Nickel and Selenium.

Method Synopsis

Twenty conditioned sticks (cigarettes) were smoked on a standard rotary smoking machine equipped with an electrostatic precipitation generator to electrostatically precipitate the particulate matter onto a glass electrostatic precipitate (EP) tube. The total particulate matter (TPM) was extracted into 25 mL methanol. The methanol extract was then evaporated using gentle heating while under a constant stream of filtered ultra high purity (UHP) nitrogen. The sample was then subjected to microwave digestion using a mixture of hydrochloric acid, nitric

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acid and hydrogen peroxide. The gaseous phase metals were trapped by placing an impinger of a 10% v/v nitric acid solution between the EP tube and the puff drawing mechanism. The impinger solution was added to the same digestion vessel as the EP tube product and subjected to microwave digestion. The digestates were then analyzed by Inductively Coupled Plasma - Mass Spectrometer (ICP-MS) or Inductively Coupled Argon Plasma - Atomic Emission Spectrometer (ICP-AES).

Method Modifications

For the analysis of "heat-not-burn" products, due to the nature of the sample, collection of the total particulate matter (TPM) required the use of two EP tubes. Each EP tube was extracted using half of the volume of methanol (12.5mL) that would have been used if only one EP tube was employed. The EP tubes and impinger samples were then collected in a single digestion vessel and subjected to the digestion process. For sample generation, sample preparation, and analysis high purity chemical reagents (Ultrapure Fisher Optima chemical grade) were used.

3.11. Mercury (T-108/TMS-00108)

Method Synopsis

Twenty conditioned sticks (cigarettes) were smoked on a standard rotary smoking machine. The mainstream smoke was passed directly through two impingers placed in series, each containing 30mL of an acidified potassium permanganate solution. The impinger solutions were then subjected to microwave digestion. Excess potassium permanganate was reduced with hydroxylamine hydrochloride and made to a final volume of 100mL. The digestate was then analyzed via cold vapour atomic absorption spectroscopy at 253.7 nm using a continuous flow vapour generator to reduce the divalent mercury to its atomic state with stannous chloride.

Method Modifications

For the analysis of "heat-not-burn" products, ten sticks were smoked per port on a standard 20 port linear smoking machine instead of a rotary smoking machine. The mainstream smoke was passed through two midget impingers, each containing 10mL of the acidified potassium permanganate solution. The final volume of samples was 50mL instead of 100mL.

3.12. Hydrogen Cyanide (T-107/TMS-00107)

Method Synopsis

Five conditioned sticks (cigarettes) were smoked per port on a standard 20 port linear smoking machine, onto a conditioned, pre-weighed 44mm glass fiber filter disc (pad), with a trap containing 0.1N NaOH located directly behind the pad. The pad was extracted with 40 mL of 0.1N NaOH on a wrist action shaker for 30 minutes. Both the pad extract and impinger trapping solutions were analyzed by an automated continuous flow colorimetric analyzer where each sample undergoes on-line dilution. Hydrogen cyanide in the sample was converted to cyanogen

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chloride by an aqueous solution of chloramine-T. The cyanogen chloride then reacted with pyridine to give glutaconic aldehyde, which, upon reaction with a pyrazolone reagent, formed a coloured complex. A single channel monitored the complex, which was quantified by comparison to an external standard calibration.
For the analysis of "heat-not-burn" products, no additional changes to the sample generation, collection or sample preparation of the base method for cigarettes were required.

3.13. Oxydes of Nitrogen (T-110/TMS-00110)

Method Synopsis

One conditioned stick (cigarette) was smoked on a standard single port smoking machine, onto a conditioned, pre-weighed 44mm glass fiber filter disc (pad). The mainstream smoke was exhausted puff by puff into an evacuated smoke mixing chamber (SMC) located directly behind the pad. The gas was mixed and, at precise and consistent intervals, an aliquot of each puff was routed by vacuum through a filter to a dual channel real time chemiluminescence nitrogen oxides analyzer where the gas stream was split immediately into two channels. In channel A, the sample stream was reacted with ozone and the resultant chemiluminescent emission was directly proportional to the NO concentration in the sample. In channel B, the sample stream was chemically reduced first by a catalytic converter and then mixed with ozone in the reaction cell where the resultant chemiluminescent emission was due to NOx or NO + NO2. Selective photomultiplier detection monitored the reaction cell gas stream and the NO and NOx found in the vapour phase of mainstream tobacco smoke were quantified by external standard calibration.

Method Modifications

For the analysis of "heat-not-burn" products, the mainstream smoke from a single stick was exhausted puff by puff into an evacuated 500mL smoke mixing chamber. Calibration was done with three levels of concentration including 9, 30, and 50 ppm (NO/NOx).

3.14. Polycyclic Aromatic Hydrocarbons [PAH] (TMS-00120)

This method is used to quantify Benzo[a]pyrene, Dibenz[a,h]anthracene, Benzo[a]anthracene and Pyrene.

Method Synopsis

Ten conditioned sticks (cigarettes) were smoked using a standard rotary smoking machine, onto a conditioned, pre-weighed 92mm glass fiber filter disc (pad). The pad was spiked with internal standards (d12-benzo[a]pyrene, d14-dibenz[a,h]anthracene, d10-anthracene and d10-pyrene) and extracted with 50 mL of methanol. The methanol extracts were filtered through a filter paper. A portion of filtered extract was cleaned up by Solid Phase Extraction (SPE) using a RapidTrace SPE Workstation and analyzed by gas chromatography-mass spectrometry for

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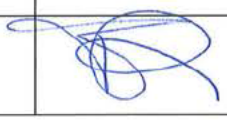
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quantification. The mass detector was operated under Selected Ion Monitoring (SIM) mode. The ions of interest (i.e. molecular ions and in some cases specific fragment ions) were mass-selected and used for quantification.

Method Modifications

For the analysis of "heat-not-burn" products, five sticks were smoked per port on a standard 20 port linear smoking machine using a 44mm pad instead of a rotary smoking machine. After adding the internal standards solution to the pad, the pad was extracted with 20mL of methanol. The sample was then analyzed by GC/MS as described above.

4. APPROVALS

	Name	Role	Signature	Date
Author	Cyril Jeannet	Manager, Product Characterization		13-Jul-2016
Owner	Serge Maeder	Director, PMI Testing Laboratories Governance		14.07.2016
QA Review	Florence Kapp	QA Officer		14 JUL 2016

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