APPENDIX A3.2.2-5

BATCH RELEASE ANALYSIS – CHEMICAL

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1. (b) (4)

1.1. Applicability

The method is used to quantitate target analytes from conventional cigarettes (3R4F) and the Tobacco Heating System (THS) consumables (Tobacco Sticks). (b) (4) :

- (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)

Results are expressed as µg/stick for THS and µg/cigarette for 3R4F.

1.2. Analytical Procedure

For batch release testing the Health Canada Intense (HCI) smoking regime is used.

For THS (b) (4) were performed by (b) (4) (b) (4) s were performed for the reference cigarettes 3R4F (b) (4) (b) (4) .

(b) (4) (b) (4) (b) (4)

(b) (4)

Preceding the analysis (b) (4) is performed according to the details given in Section 1.2.3. (b) (4)).

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1.2.1. Preparation of Solutions

1.2.1.1. Calibration Solutions

(b) (4)

(b) (4) provided in Table 1.

Table 1: Calibration Standard Ranges

(b) (4)

1.2.2. Experimental Conditions

1.2.2.1. Equipment

Gas chromatograph	A suitable GC with a MS detector and data acquisition software
Pre-column	Deactivated silica 2 m x 0.25 mm x 0.25 µm film thickness
Capillary column	30 m x 0.25 mm x 0.5 µm film thickness

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1.2.2.2. Chromatographic Conditions

Injection temperature	250°C
Injection volume	0.5 µL
Carrier gas	Helium, pulsed splitless injection
Temperature program	65°C, hold 0.5 min Heating to 175°C, 7°C/min Heating to 260°C, 15°C/min, hold 8 min

1.2.2.3. Mass Spectrometer Settings

MS Quad temperature	150ºC
Ion source temperature	230ºC
Acquisition type	Single-ion monitoring

1.2.3. Calibration

Calibration is performed with (b) (4) (b) (4) s listed in Table 1. A ratio of each compound to the internal standard is determined and a linear regression is performed against concentration for each compound, with statistical weights of 1/concentration, according to:

$$\frac{A_a}{A_{iStd}} = p \times C_a + b$$

where

A_a area of target analyte

A_{iSD} area of corresponding internal standard

C_a concentration of target analyte

b intercept

p slope

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Calibration is considered valid (b) (4)

1.2.4. Example Chromatogram

An example chromatogram is provided in Figure 1.

(b) (4)

Figure 1: Example Chromatogram

1.2.5. Retention Times

Typical retention times for the compounds and internal standards are provided in Table 2.

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Table 2: (b) (4)

(b) (4)

1.2.6. System Suitability

(b) (4) The acceptance criteria are provided in Table 3.

Table 3: System Suitability Acceptance Criteria

(b) (4)

1.3. Validation

1.3.1. Specificity (Selectivity)

(b) (4)

- (b) (4)
- (b) (4)

(b) (4)

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- (b) (4)
- (b) (4)

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1.3.2. Linearity

The linearity of the response functions was demonstrated for the range of concentrations spanned by the calibration solutions (Table 4). (b) (4)

(b) (4)

Figure 2: (b) (4)

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Figure 3: (b) (4)



Figure 4: (b) (4)

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Figure 5: (b) (4)



Figure 6: (b) (4)

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Figure 7: (b) (4)

1.3.2.1. Calibration Curve Parameters

Calibration curve parameters using the selected regression model (linear regression with 1/concentration weighing) were evaluated. The average slope, intercept, and coefficient of variation for each compound are provided in Table 4. The acceptance criteria were met in all cases.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

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(b) (4) 1.2.3) (b) (4)
(b) (4)

Table 4: (b) (4))

(b) (4)

(b) (4)

1.3.3. Range

(b) (4)

(b) (4)

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(b) (4)

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Figure 8: Example of an (b) (4)

(b) (4) are provided in Table 5.

Table 5: (b) (4)



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1.3.4. Accuracy and Precision

1.3.4.1. Repeatability

Results (b) (4) repeatability limits (b) (4) (b) (4) t are provided in Table 6: (b) (4) (b) (4).

Table 6: (b) (4) Repeatability (b) (4)

	3R4F (µg/cig)				THS (µg/stick)			
	Mean	SD	CV	r	Mean	SD	CV	r
(b) (4)								

SD = standard deviation, CV = Coefficient of variation, r = correlation coefficient

Repeatability was assessed by evaluation of (b) (4) The results are given in **Table 7**. (b) (4) (b) (4).

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Table 7: Repeatability Limit in (b) (4)

	3R4F (µg/cig)				THS (µg/stick)			
	Mean	SD	CV	r	Mean	SD	CV	r
(b) (4)								

SD = standard deviation, CV = Coefficient of variation, r = correlation coefficient

1.3.4.2. (b) (4) Precision Limit

The (b) (4) precision limit was evaluated by (b) (4)
(b) (4)
precision limits are provided in **Table 8**.

Table 8: (b) (4) Precision Limit (b) (4)

	3R4F (µg/cig)				THS (µg/stick)			
	Mean	SD	CV	IP	Mean	SD	CV	IP
(b) (4)								

SD = standard deviation, CV = Coefficient of variation, IP = intermediate precision

1.3.4.3. Reproducibility

(b) (4) .

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1.3.4.4. Combined Uncertainty

(b) (4)

(**Table 9**).

Table 9: Combined Uncertainty (b) (4)

(b) (4)

1.3.5. Limit of Detection (LOD)/Limit of Quantitation (LOQ)

The limit of detection and lower limit of quantitation (LLOQ) are both calculated in terms of the standard deviation of the lowest calibration level as determined during validation,

$$LOD = 3 \cdot std_{level1}$$

$$LOQ = 10 \cdot std_{level1}$$

They were found to be lower than the concentration of the lowest calibration level for all compounds. Detailed results are provided in Table 10.

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Table 10: Limits of Detection and Quantitation

	3R4F (µg/cig)			THS (µg/stick)		
	LOD	LLOQ	ULOQ	LOD	LLOQ	ULOQ
(b) (4)						

ULOQ = upper limit of quanititation (highest standard level)

1.3.6. Robustness

(b) (4)
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(b) (4)
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Note: (b) (4) method is currently under evaluation (b) (4)
(b) (4)
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2. (b) (4)

2.1. Description of Method

(b) (4)

3. APPROVALS

	Name	Role	Signature	Date
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QA Review	Florence Kapp	QA Officer Audit		26Jul16

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