APPENDIX A3.3-8 (V2)

STABILITY FINAL RESULTS (12 MONTHS) – MENTHOL 1

Confidentiality Statement

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REPORT OF THE STABILITY STUDY FOR DORADO I MINT VINNY LOW THS 2.2 (EXPT004923)

Platform	P1

Stability Study type	Initial Stability Study	☐
	In use	☐
	Post Change	☒
	Monitoring	☐

Name	Role	Justification	Date (dd-Mon-yyyy)	Signature
Rita Hajdu Schenk	QC Unit Coordinator	Author	09-Nov-2017	
Céline Bies	QC Unit Statistician	Author	09-NOV-2017	
Hyun Buclin	Quality Assurance Quality Control	Reviewer	09-NOV-2017	
Shelley Moores	Quality Assurance	Reviewer	09-NOV-2017	
Cyril Jeannet	Head of QC Unit	Approver	13-NOV-2017	

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1 Purpose

The objective of this stability study is to demonstrate that the commercial product THS 2.2 Low Menthol (Dorado I Mint Vinny) version (Platform 1) produced at Philip Morris Manufacturing & Technology Bologna (PMMTB) remains within product specifications over the determined shelf life period, when stored under the defined WHO (30 ± 2ºC; 75 ± 5% RH and 30 ± 2ºC 35 ± 5% RH) and ISO (22 ± 2°C; 60 ± 5% RH) storage conditions.

This report summarizes the results and trend analysis of the stability study STAB-2016_P1_M_1 performed according a protocol [1]. The study was performed in 3 production scale Dorado I Mint Vinny Low batches.

(b) (4)

The Evaluation of the stability data was performed according the description in the procedure PMI_RD_SOP_000296 Perform Stability Studies and in line with ICH Q1(E) Evaluation of Stability Data.

2 Batches

Table 1 Identification of THS 2.2 Dorado I Vinny Low

Product/ Test item	Consumable Batch Number	Finished Product Code	Manufacturing Date
THS 2.2 Dorado I Vinny Low	B-25900 / 41.2381531	ME000041.01	21 Dec. 2015
	B-25901 / 41.2374718	ME000041.01	22 Dec. 2015
	B-25902 / 41.2379112	ME000041.01	16 Dec. 2015

The samples were stored in the climatic chambers in packs. The packs are polypropylene wrapped and consists of two collation, each collation containing 10 Heat sticks.

3 Tests Methods and Specifications

3.1 Preparation and Conditioning

The 3R4F Reference Cigarette (purchased from the University of Kentucky) or P1 monitor (P1M1) was used as an internal monitor for aerosol chemistry and values were compared to respective upper and lower limit defined in the control charts to verify the correct functioning of the experimental setup.

At each time point before aerosol analyses, in order to perform the testing under normal conditions as on freshly made products, sticks were reconditioned outside of the packs following ISO standard 3402 (1999), at least 48 hours at 22 ± 1 °C, 60 ± 3% RH prior to aerosol generation. For the determination of the Menthol in the aerosol, sticks were kept in closed packs prior analyses in order to avoid loss of menthol.

Conditioning for physical analyses was performed as described in respective work instruction, inside open packs for at least 24 hours at 22 ± 2 °C and 50 ± 5% RH.

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Sticks were kept in closed pack at 22°C ± 2°C and 58% RH ± 5% prior sensorial evaluation.

Visual evaluation was performed on sticks received in close packs without any preliminary preparation.

3.2 Aerosol Generation and Analyses

The atmosphere for aerosol generation was 22 ± 2°C, 60 ± 5% RH.

Aerosol generation was performed on Borgwaldt linear smoking machines.

The Health Canada Intense (HCI) smoking regimen using bell shaped puff profile was used with the below listed parameters to generate the aerosol for further chemical analyses:

- Puff volume: 55 mL
- Puff duration: 2.0 s
- Puff interval: 30 s
- Number of puffs: 12

All the instruments and material are listed in the relevant work instructions in Table 2.

The tobacco heating device DV.000174 was used to generate aerosol for chemical analyses and device DV.000101.RD was used for sensorial evaluation (b) (4)

Table 2 Tests, Methods and Specifications

Parameter	Method Name	Method Version Planned	Method Version Used T0 / T12	Specifications [2] -[4]
Nicotine mg/stick	PMI_RD_WKI_000530 PMI_RD_WKI_000953	7.0 3.0	7.0 / 8.0 3.0 / 3.0	(b) (4)
Glycerin mg/stick	PMI_RD_WKI_000530 PMI_RD_WKI_000953	7.0 3.0	7.0 / 8.0 3.0 / 3.0	
CO mg/stick	PMI_RD_WKI_000530	7.0	7.0 / 8.0	
Triacetin mg/stick	PMI_RD_WKI_000530 PMI_RD_WKI_000953	7.0 3.0	7.0 / 8.0 3.0 / 3.0	
Menthol mg/stick	PMI_RD_WKI_000530 PMI_RD_WKI_000953	7.0 3.0	7.0 / 8.0 3.0 / 3.0	
TPM mg/stick	PMI_RD_WKI_000530	7.0	7.0 / 8.0	
Phenol µg/stick	PMI_RD_WKI_000530 PMI_RD_WKI_000953	7.0 3.0	7.0 / 8.0 3.0 / 3.0	
Acrylamide µg/stick	PMI_RD_WKI_000530 PMI_RD_WKI_000953	7.0 3.0	7.0 / 8.0 3.0 / 3.0	

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Parameter	Method Name	Method Version Planned	Method Version Used T0 / T12	Specifications [2] -[4]
Acetamide	PMI_RD_WKI_000530	7.0	7.0 / 8.0	(b) (4)
µg/stick	PMI_RD_WKI_000584	7.0	7.0 / 7.0	
Acetaldehyde	PMI_RD_WKI_000534	11.0	11.0 / 12.0	
µg/stick	PMI_RD_WKI_000391	13.0	13.0 / 15.0	
Butyraldehyde	PMI_RD_WKI_000534	11.0	11.0 / 12.0	
µg/stick	PMI_RD_WKI_000391	13.0	13.0 / 15.0	
Acrylonitrile	PMI_RD_WKI_000518	7.0	7.0 / 7.0	
µg/stick	PMI_RD_WKI_000383	15.0	15.0 / 17.0	
Isoprene	PMI_RD_WKI_000518	7.0	7.0 / 7.0	
µg/stick	PMI_RD_WKI_000383	15.0	15.0 / 17.0	
Pyridine	PMI_RD_WKI_000518	7.0	7.0 / 7.0	
µg/stick	PMI_RD_WKI_000383	15.0	15.0 / 17.0	
Ammonia	PMI_RD_WKI_000385	10.0	10.0 / 10.0	
µg/stick	PMI_RD_WKI_001392	1.0	1.0 / 2.0	

(b) (4)

(b) (4)

3.3 Visual Inspection

(b) (4)

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3.4 Sensorial Evaluation

(b) (4)

4 Stability Study Design

Table 3 Testing Matrix

Batch	Storage Conditions	Beginning of the Study *	Analysis Time Points (months)					
			0	2	4	6	9	12
Dorado I Vinny Low (B-25900)	22ºC±2ºC / 60%RH±5%RH	January 22, 2016	M P S PF		M P S	M P S PF		M P S PF
	30ºC±2ºC / 75%RH±5%RH			M P S	M P S		C**	C**
	30ºC±2ºC / 35%RH±5%RH			M P S		M P S PF	M P S PF	M P S PF
Dorado I Vinny Low (B-25901)	22ºC±2ºC / 60%RH±5%RH	January 22, 2016	M P S PF	M P S	M P S		M P S PF	M P S PF
	30ºC±2ºC / 75%RH±5%RH			M P S		M P S PF	C**	C**
	30ºC±2ºC / 35%RH±5%RH				M P S	M P S PF		M P S PF
Dorado I Vinny Low (B-25902)	22ºC±2ºC / 60%RH±5%RH	January 22, 2016	M P S PF	M P S		M P S PF	M P S PF	M P S PF
	30ºC±2ºC / 75%RH±5%RH				M P S	M P S PF		C**
	30ºC±2ºC / 35%RH±5%RH			M P S	M P S		M P S PF	M P S PF

M: Batch release parameters, acrylonitrile, isoprene; P: Physical measurements: diameter and visual inspection; S: Sensorial analysis; PF: All performance parameters

* Beginning of the study corresponds to the date when the packs were put in the climatic chambers.

** Analyses at T9 and T12 for the conditions 30°C 75%RH were cancelled, decision based on visual aspect not acceptable at T4 and T6.

The number of replicates performed per analyses were as follows:

- T0 and T12 aerosol: 6 replicates/batch; (b) (4)   : 50 sticks/batch; Visual evaluation: 100 sticks/batch

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- T2 – T9 - aerosol: 4 replicates/batch (b) (4)   : 50 sticks/batch; Visual evaluation: 100 sticks/batch

5 Deviations to Study Protocol

5.1 Deviation in Storage Condition

Due to breakdown of the conditioning system for 22°C 60%RH, the relative humidity was not stable and was out of the tolerance from 24 Dec. 2016 to 30 Dec. 2016 with a mean value of 52.2%RH. The non-conformity is documented in RLS-TIM-17-1. The out of tolerance happened approximately 1 month before T12 time point and represent ~5% below the lower range limit.

5.1.1 Impact on the Study

In dry condition, 30°C 35%RH, the product remain in specification at T12. As the packs are stored in the climatic chambers in polypropylene wrapped packs and as no out of trend was observed as T12, it is considered that the product was not affected by this non-conformity in this period of time.

5.2 Deviation in Methods

The version of some of the methods changed during the study compared to what was described in the study protocol (Table 2). The change in the versions reflects only changes with no impact on the quantification for the all methods, except for Isoprene (PMI_RD_WKI_000383).

The version of the method changed from V15 to V16 between the T0 and the T2 (18 Feb. 2016) due to implementation of Certified Reference Materials. The change was considered at the time as having no impact on the quantification of the compounds of the method, involving Isoprene, Acrylonitrile and Pyridine from the stability studies.

An out of trend investigation was opened for Isoprene at T6 for the conditions 22°C 60%RH and 30°C 35%RH and observed that the 3R4F monitor had similar increasing trend as the samples from the stability study indicating that the increase was not product related. A laboratory investigation [6] was performed and confirmed that switching from V15 to V16 had an impact on the quantification for Isoprene only and that the values generated from 18 Feb. 2016 to 25 Oct. 2016 tend to be overestimated, however no constant bias could be determined.

It was then decided to revert back to the reference material used prior to February 2016 described in PMI_RD_WKI_000383 V15 which provided more consistent results regarding Isoprene quantitation than those used after that date. This change was implemented in PMI_RD_WKI_000383 V17 effective as of 25 Oct. 2016, just prior the analyses for T9 time point.

The method (PMI_RD_WKI_000383) versions per time point are summarized in Table 4.

Table 4 PMI_RD_WKI_000383 Versions per Time Point

STAB-2016_P1_M_1	Time Points (months)					
	0	2	4	6	9	12
Version of the method PMI_RD_WKI_000383	V15.0	V16.0	V16.0	V16.0	V17.0	V17.0

5.2.1 Impact on the Study

The change in the method during the stability study has an impact on the evaluation of results for Isoprene.

The stability specifications were set by using the T0 values obtained with method V15. As during three intermediate time-points (T2, T4 and T6) the quantification of Isoprene was performed with method V16 and consequently overestimated, the results of these time point cannot be used for the evaluation.

Therefore, for storage conditions 22°C 60%RH and 30°C 35%RH only the reported value from T9 and T12 are used for evaluation. As the degradation of Isoprene was following a linear trend in previous stability studies it is considered covering the worst case by evaluating T9 and T12. Results from T2 to T6 are not reported.

For the storage condition 30°C 75%RH for which analyses were performed only until T6, the reported values from T2 to T6, obtained with the method V16, are checked against the specification, which covers as well the worst case knowing that these values are overestimated.

5.3 Deviation in Study Design

The analyses for T9 and T12 time point for the tropical 30°C 75%RH condition (Climatic Zone IVB) were cancelled, decision based on the visual aspect of the sticks found not acceptable at T4 and T6.

5.3.1 Impact on the Study

The data evaluation for this condition was performed with the results from T0 to T6, trend analyses was not performed when results were available for less than 3 time point. The reported values are checked against the specifications as described in Chapter 6.3.

6 Stability Data Evaluation

The statistical analysis for the chemical and physical characterization is performed according PMI_RD_SOP_000296, following ICH Q1E and is mainly performed by modelling the degradation profile of the test parameters by using regression models. The regression analysis defines the trend of a quantitative stability test parameter for each batch over time on the predetermined stress conditions. The regression analysis is only performed for parameters for which a minimum of 3 time points data is available and data is suitable for trend analyses. For the other parameters having less than 3 data points, the reported value (mean) is compared versus the specification.

The Tables 5 - 13 contain for each batch and for each tested parameter per time point the reported values, together with the specifications. When only Upper specification exists the fields for the Lower specifications are marked in gray. The fields for the "Time points" are marked in gray when no analyses were performed by study design or results are not reported (i.e. Isoprene value -see Deviation in Chapter 5.2).

The relative degradation rate, the R^2 and the severity scores are provided for information only and for parameters with at least 3 time points available (NA –is written when it's is not applicable).

The Figures 1 - 48 contain the reported values for the 3 batches together with the upper and/or lower specification levels (USL and LSL), the linear regression of the 3 batches if applicable and the upper and lower 95 % confidence intervals for the regression mean (UMCI and LMCI). The Figure titles contain the

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conclusion about the shelf life obtained with (b) (4)   in case of trend analyses or conclusion about shelf life by comparing the reported value with the specification.

The shelf life obtained with (b)   is truncated to whole number. In case the shelf life calculated by (b)   is longer than the study duration than the shelf life will be equal to the study duration.

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6.1 Storage Condition 22°C 60% RH

Table 5 B-25900 / 41.2381531 at 22°C 60% RH

B-25900 / 41.2381531	Unit	Specifications		Time point (Months)						Degradation Rate	R^2	Severity Score
Test		Lower	Upper	0	2	4	6	9	12			
Menthol	mg/stick	(b) (4)		1.25		1.78	1.75		1.79	2.79%	0.57	1.6
Nicotine	mg/stick			1.17		1.12	1.17		1.13	-0.22%	0.26	0.1
Glycerin	mg/stick			4.68		4.67	4.76		4.22	-0.81%	0.64	0.5
CO	mg/stick			0.3		0.6	0.4		0.3	-0.95%	0.03	0.0
Triacetin	mg/stick			0.5		0.5	0.5		0.4	-2.01%	0.94	1.9
Phenol	µg/stick			1.2		1.5	1.4		1.1	-0.71%	0.06	0.0
Acrylamide	µg/stick			1.4		1.5	1.7		1.3	-0.17%	0.01	0.0
Acetamide	µg/stick			3.0			3.0		2.9	-0.21%	0.69	0.1
Acetaldehyde	µg/stick			205			191		199	-0.26%	0.20	0.1
Butyraldehyde	µg/stick			13.9			12.3		12.7	-0.70%	0.48	0.3
Acrylonitrile	µg/stick			0.16		0.16	0.15		0.13	-1.34%	0.89	1.2
Isoprene	µg/stick			1.59					1.46	NA	NA	NA
Pyridine	µg/stick			8.6			8.4		6.6	-1.92%	0.82	1.6
Ammonia	µg/stick			12.3			10.4		9.7	-1.75%	0.94	1.6
TPM	mg/stick			54		53	54		50	-0.63%	0.73	0.5

(b) (4)

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Table 6 B-25901 / 41.2374718 at 22°C 60% RH

B-25901 / 41.2374718	Unit	Specifications		Time point (Months)						Degradation Rate	R^2	Severity Score
Test		Lower	Upper	0	2	4	6	9	12			
Menthol	mg/stick	(b) (4)		1.23	1.85	2.04		2.09	1.87	2.59%	0.35	0.9
Nicotine	mg/stick			1.23	1.25	1.19		1.16	1.20	-0.38%	0.46	0.2
Glycerin	mg/stick			4.53	5.08	4.66		4.46	4.60	-0.38%	0.14	0.1
CO	mg/stick			0.3	0.3	0.6		0.5	0.3	1.00%	0.02	0.0
Triacetin	mg/stick			0.5	0.6	0.5		0.5	0.5	-1.19%	0.48	0.6
Phenol	µg/stick			1.2	1.7	1.3		1.4	1.4	0.12%	0.00	0.0
Acrylamide	µg/stick			1.4	1.6	1.5		1.4	1.5	0.24%	0.05	0.0
Acetamide	µg/stick			3.2				3.1	3.2	-0.23%	0.58	0.1
Acetaldehyde	µg/stick			195				186	205	0.21%	0.07	0.0
Butyraldehyde	µg/stick			13.4				13.1	12.6	-0.46%	0.87	0.4
Acrylonitrile	µg/stick			0.17	0.16	0.16		0.14	0.15	-0.99%	0.62	0.6
Isoprene	µg/stick			1.72				1.60	1.70	-0.24%	0.16	0.0
Pyridine	µg/stick			8.7				8.9	7.2	-1.05%	0.41	0.4
Ammonia	µg/stick			12.5				11.0	10.4	-1.36%	1.00	1.4
TPM	mg/stick			56	57	53		53	52	-0.72%	0.79	0.6

(b) (4)

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Table 7 B-25902 / 41.2379112 at 22^{0}C 60% RH

B-25902 / 41.2379112	Unit	Specifications		Time point (Months)						Degradation Rate	R^2	Severity Score
Test		Lower	Upper	0	2	4	6	9	12			
Menthol	mg/stick	(b) (4)		1.05	1.68		1.89	1.97	1.76	3.84%	0.51	1.9
Nicotine	mg/stick			1.22	1.13		1.17	1.10	1.15	-0.40%	0.27	0.1
Glycerin	mg/stick			4.59	4.60		4.43	4.13	4.08	-1.04%	0.93	1.0
CO	mg/stick			0.3	0.3		0.4	0.5	0.3	2.26%	0.22	0.5
Triacetin	mg/stick			0.5	0.5		0.5	0.4	0.4	-1.51%	0.88	1.3
Phenol	µg/stick			1.3	1.2		1.2	0.9	1.0	-2.15%	0.72	1.6
Acrylamide	µg/stick			1.4	1.3		1.6	1.3	1.3	-0.60%	0.09	0.1
Acetamide	µg/stick			3.0			3.0	2.8	2.5	-1.34%	0.75	1.0
Acetaldehyde	µg/stick			195			200	177	198	-0.21%	0.04	0.0
Butyraldehyde	µg/stick			13.4			13.1	12.1	12.8	-0.57%	0.52	0.3
Acrylonitrile	µg/stick			0.16	0.14		0.17	0.13	0.14	-0.97%	0.22	0.2
Isoprene	µg/stick			1.66				1.49	1.41	-1.21%	1.00	1.2
Pyridine	µg/stick			8.6			9.1	8.6	7.2	-1.03%	0.36	0.4
Ammonia	µg/stick			12.0			10.6	10.6	9.2	-1.72%	0.91	1.6
TPM	mg/stick			56	54		55	53	51	-0.57%	0.72	0.4

(b) (4)

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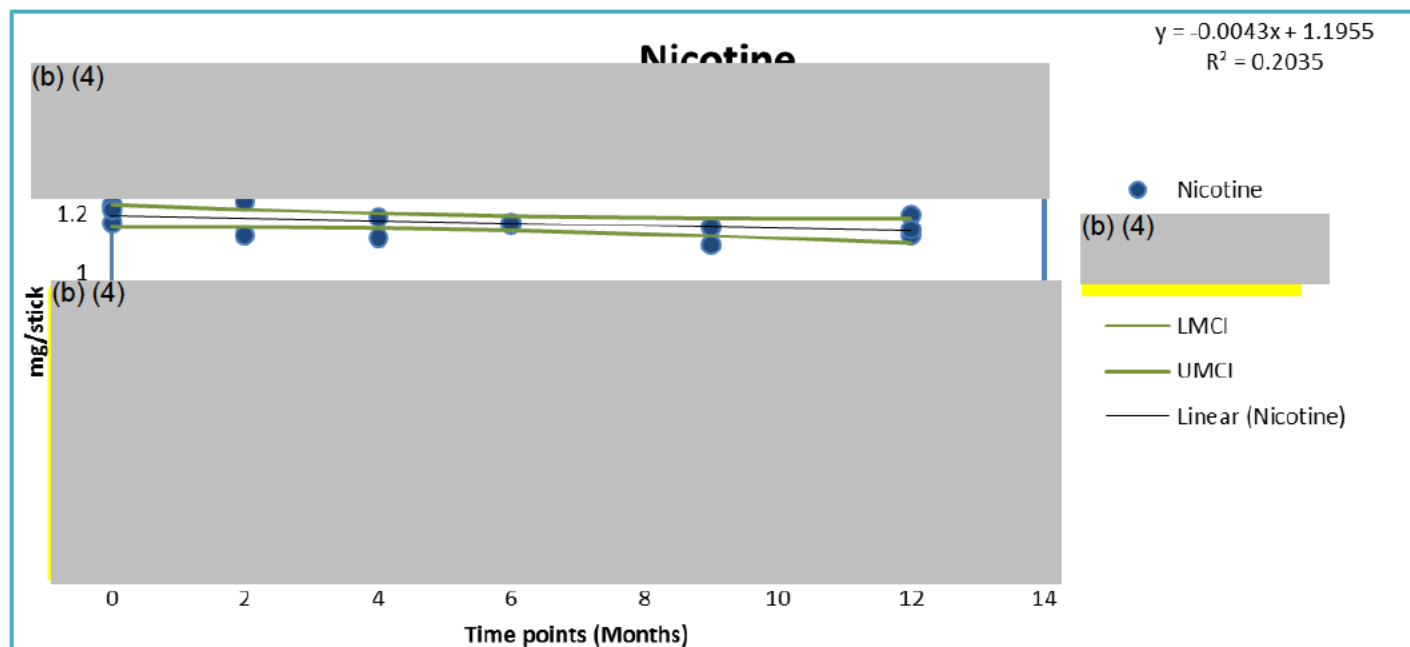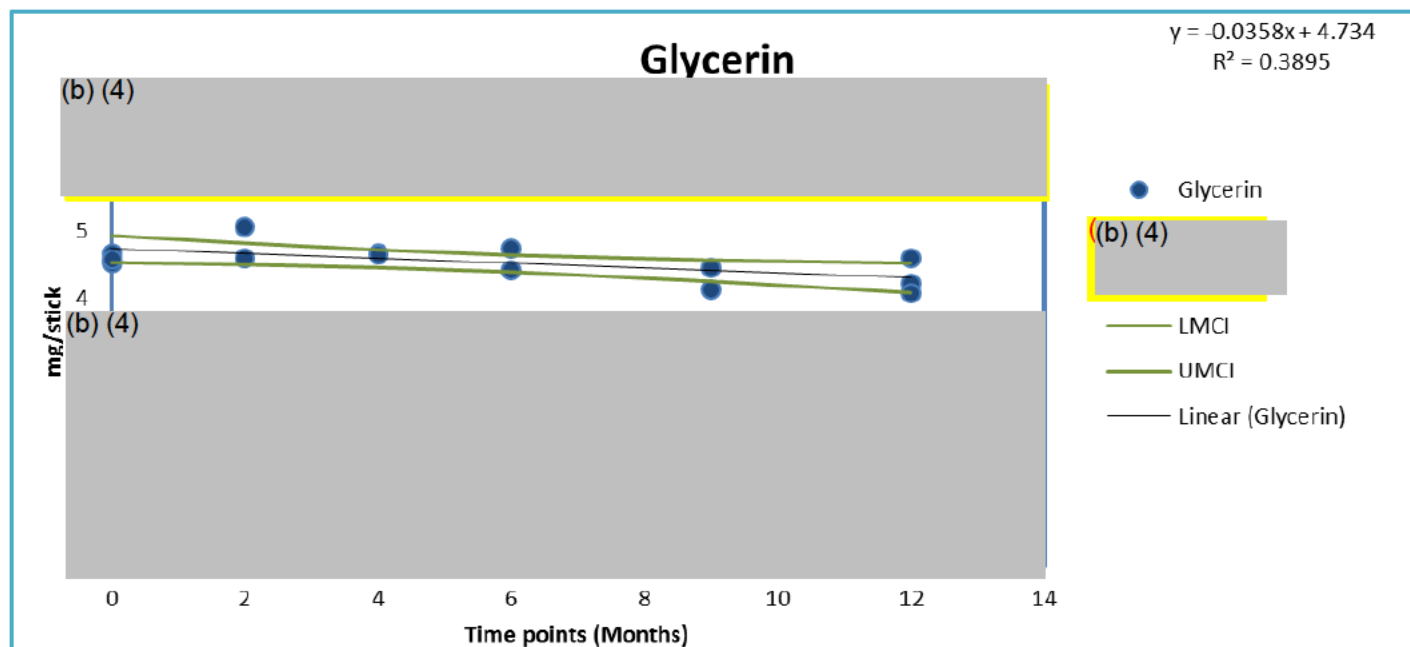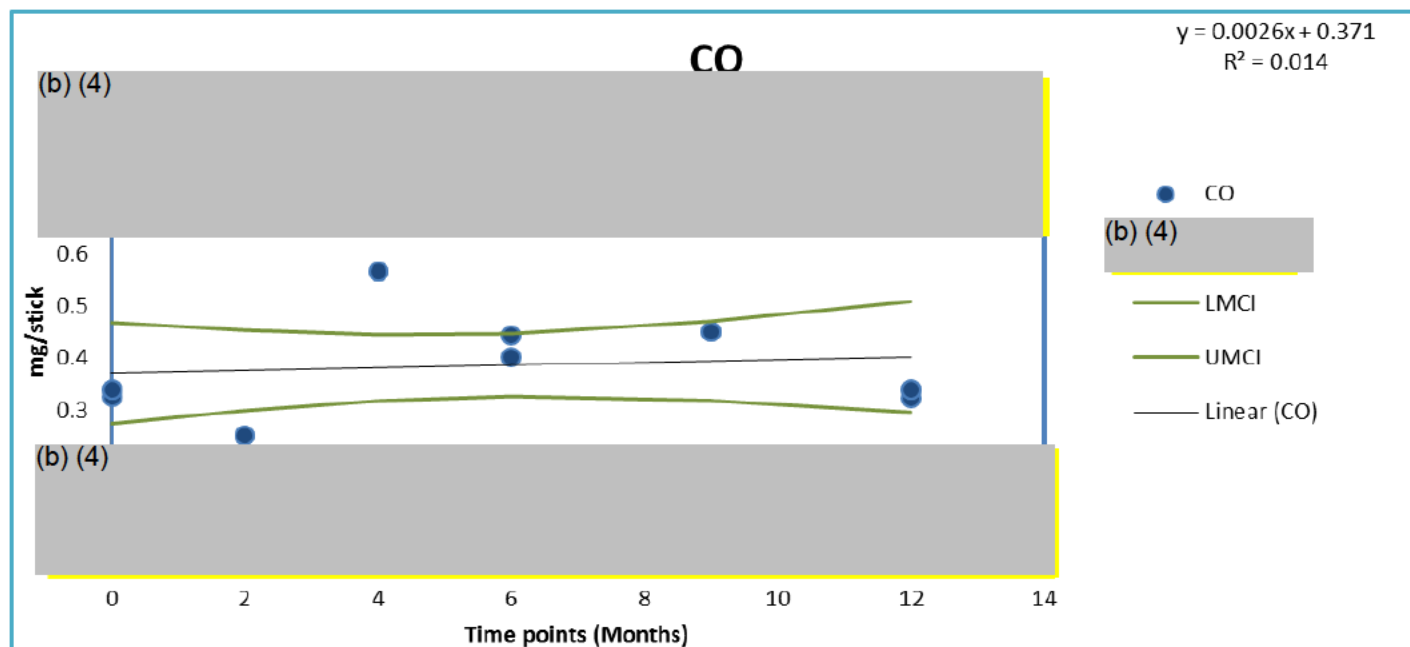
6.1.1 Mainstream Aerosol Evaluation

6.1.1.1 Menthol

Figure 1 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.
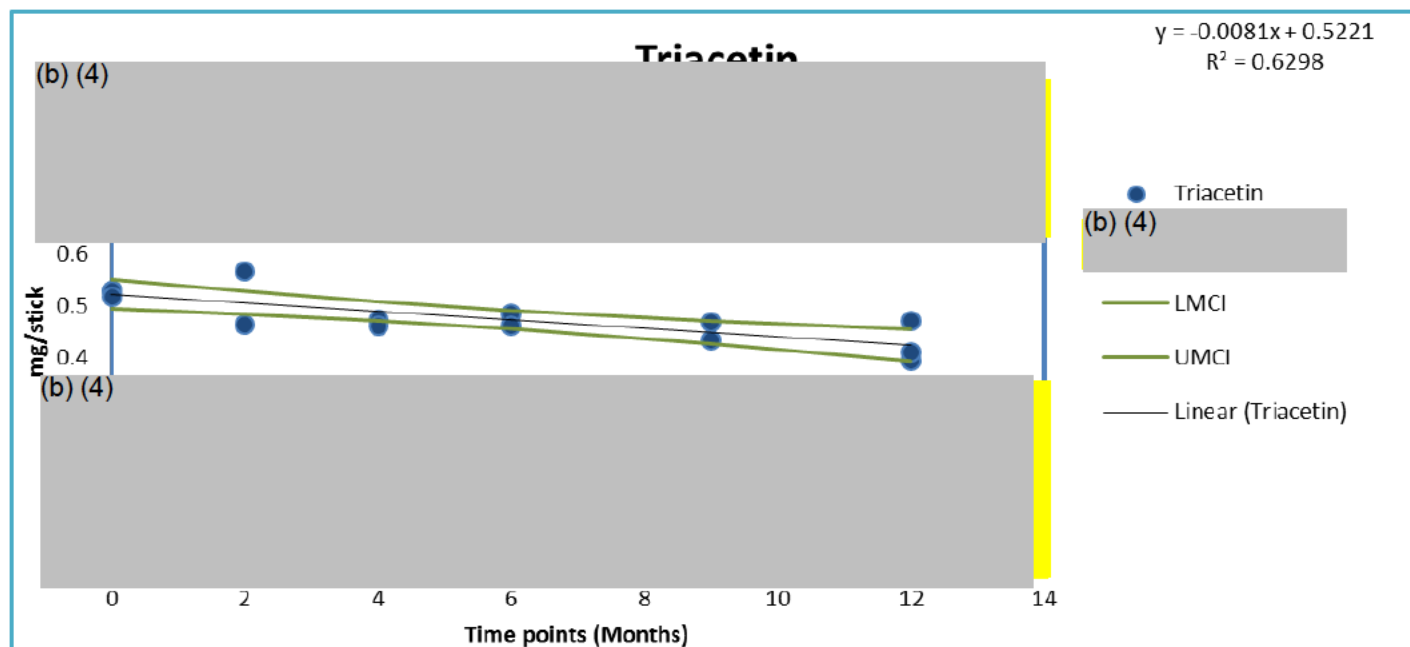
6.1.1.2 Nicotine

Figure 2 The best model accepted at the significance level of 0.25 has Different intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.

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6.1.1.3 Glycerin

Figure 3 The best model accepted at the significance level of 0.25 has Different intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.

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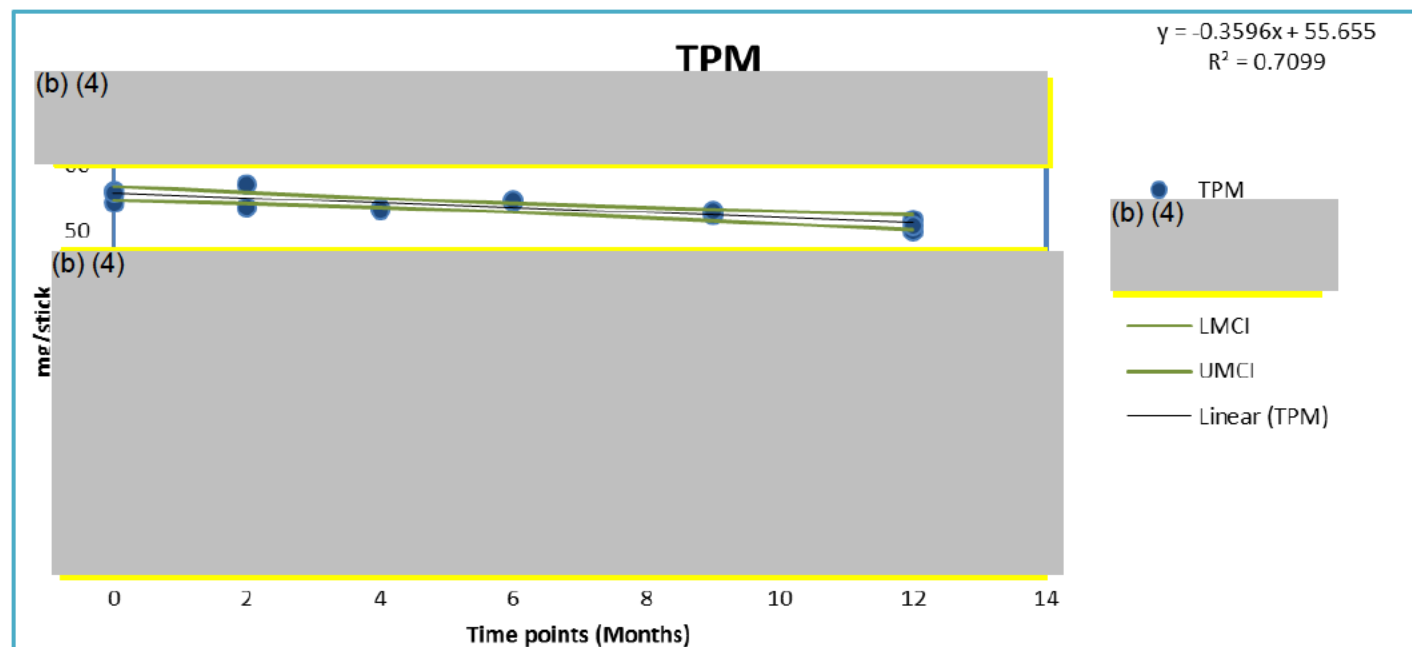Form Effective Date: See EDMS

6.1.1.4 CO

Figure 4 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.

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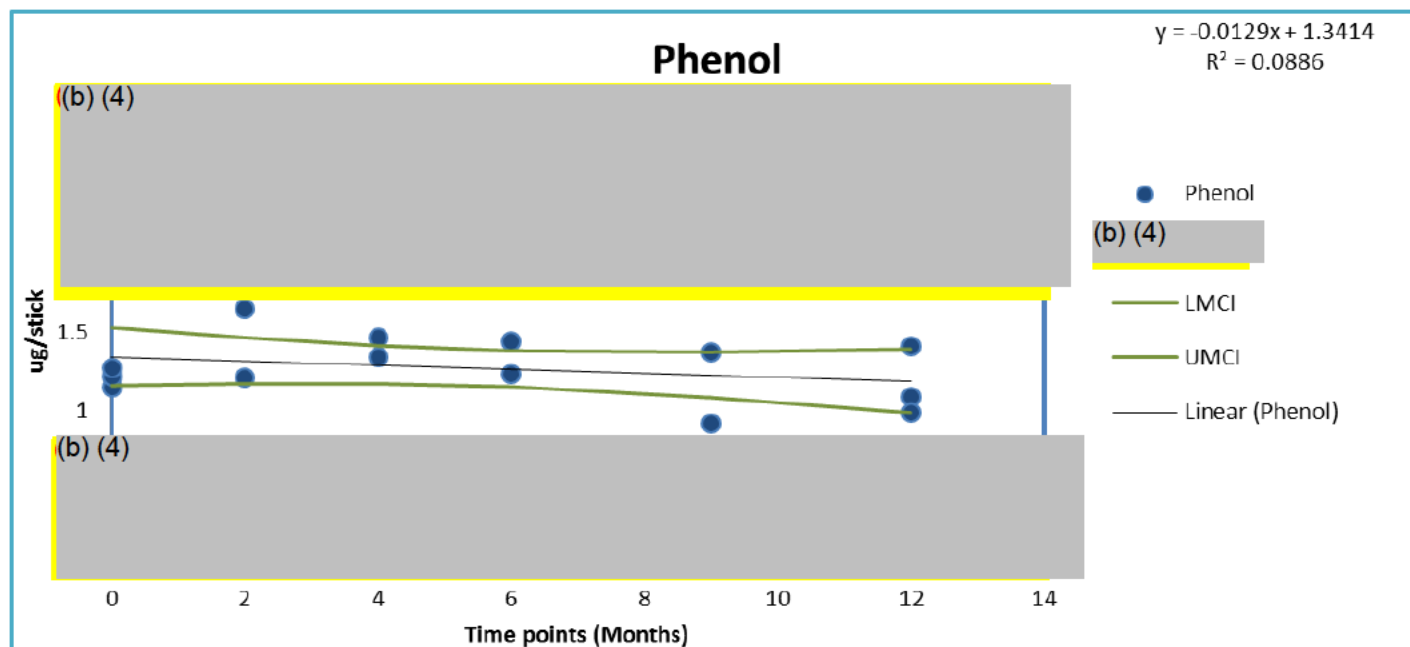
6.1.1.5 Triacetin

Figure 5 The best model accepted at the significance level of 0.25 has Different intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.

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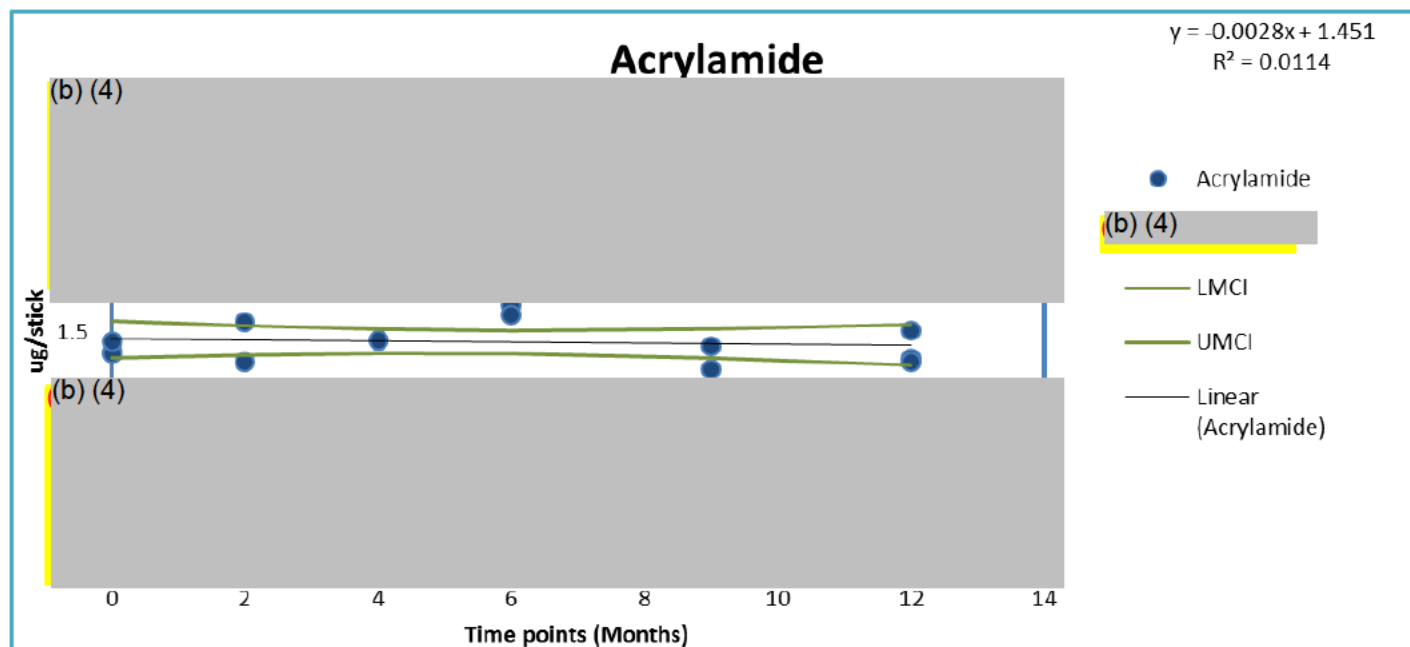### 6.1.1.6 TPM

$$y = -0.3596x + 55.655$$
$$R^2 = 0.7099$$

Figure 6 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.

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6.1.1.7 Phenol

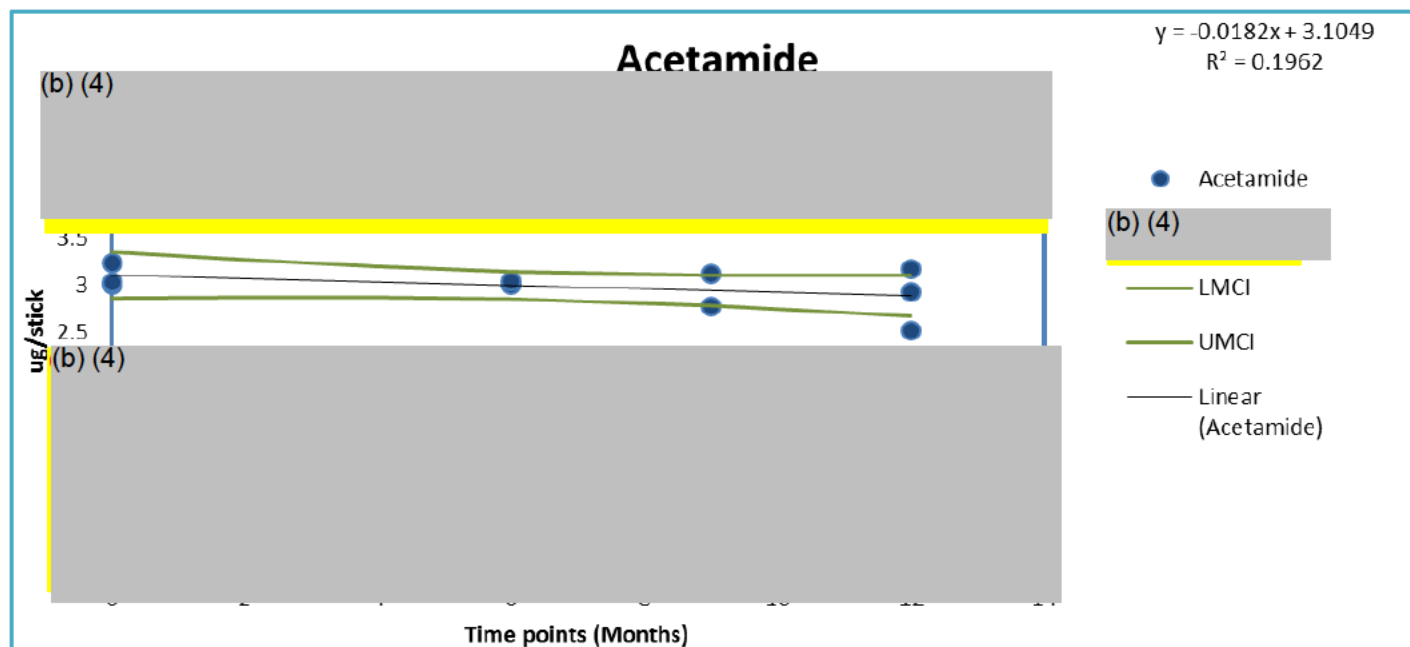
Figure 7 The best model accepted at the significance level of 0.25 has Different intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.

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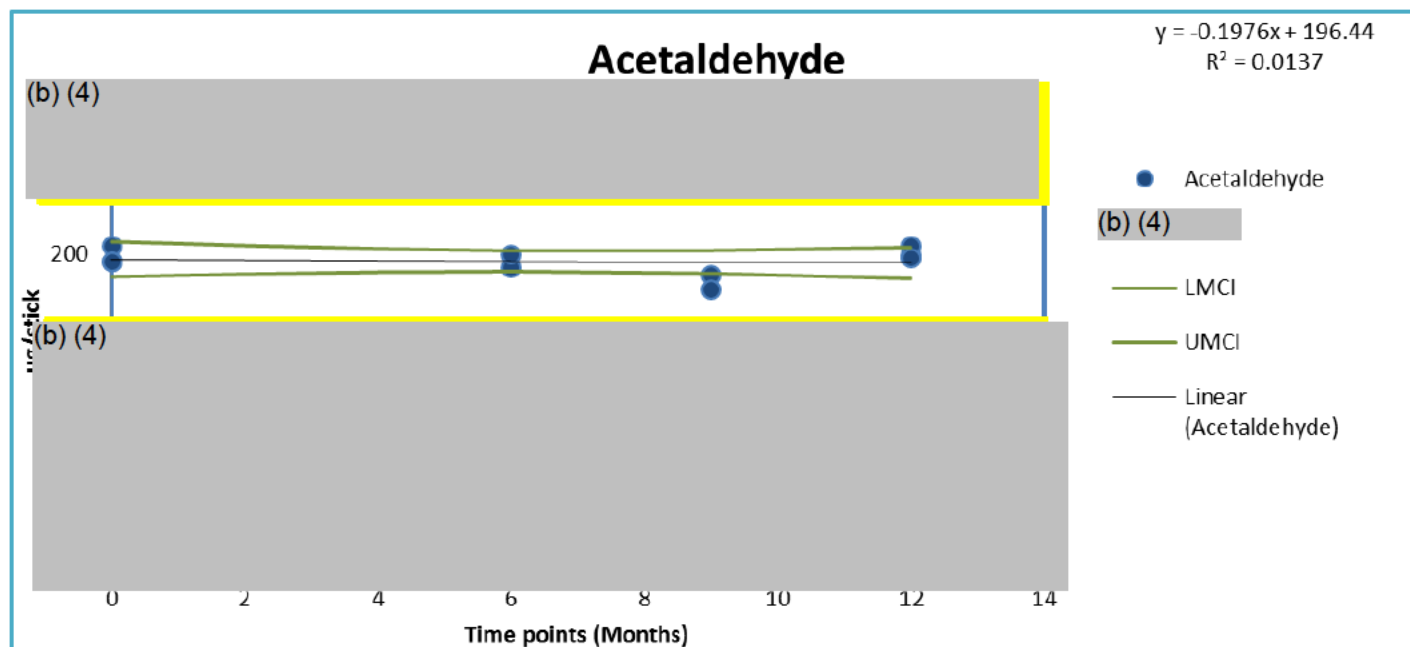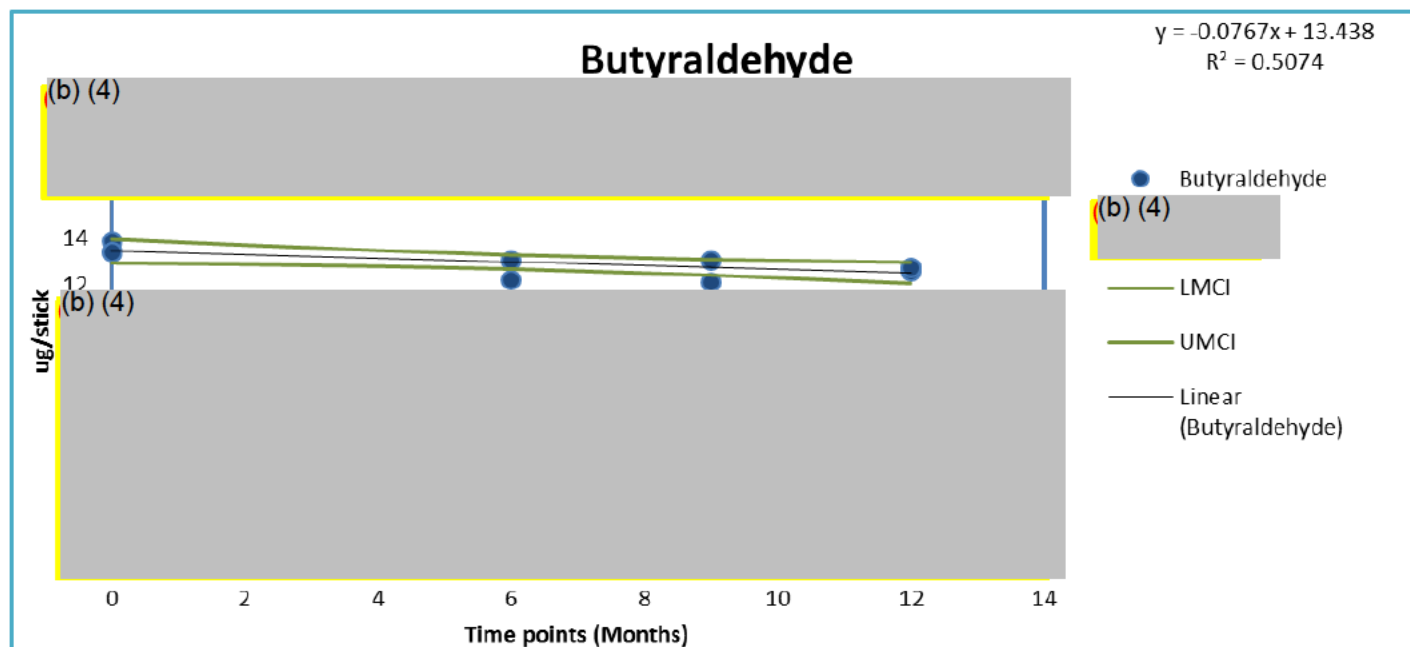| Form Number: PMI_RD_FOR_000927	Form Version N°: 1.0	Form Status: Effective
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6.1.1.8 Acrylamide

Figure 8 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.

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6.1.1.9 Acetamide

Figure 9 The best model accepted at the significance level of 0.25 has Different intercepts and Different slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.

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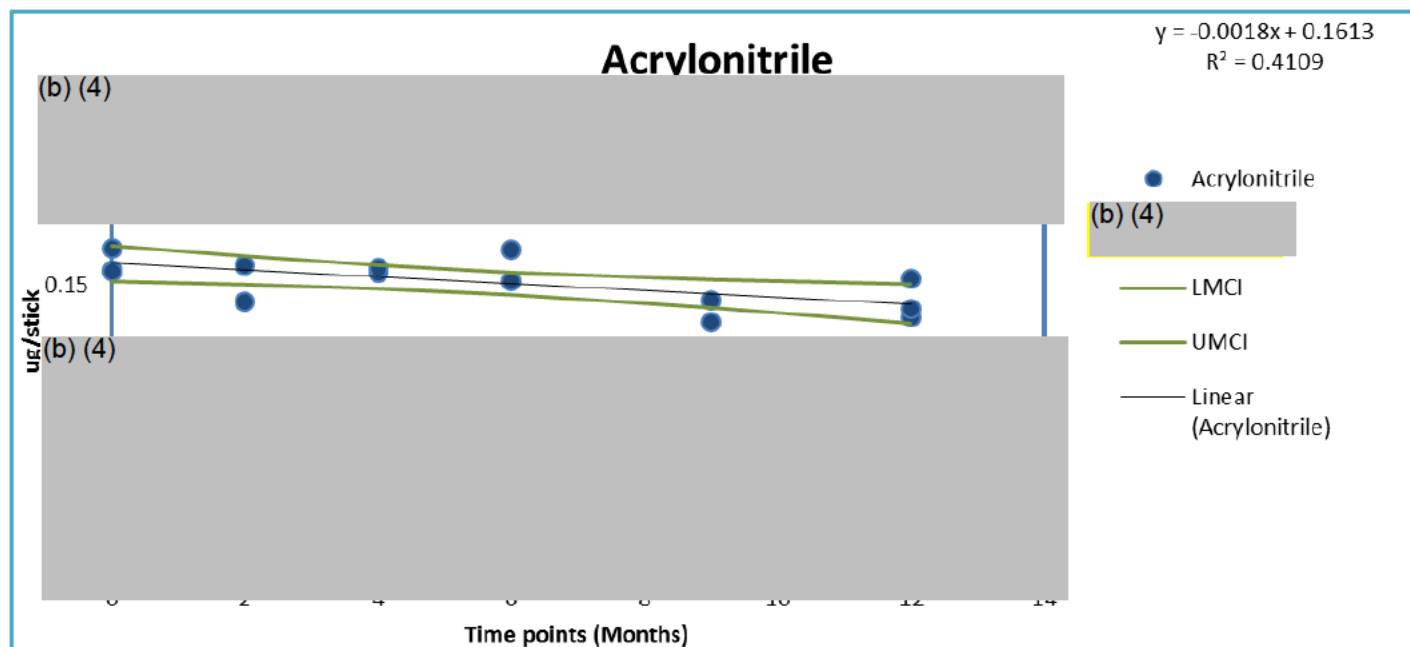|		
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6.1.1.10 Acetaldehyde

Figure 10 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.

6.1.1.11 Butyraldehyde

Figure 11 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.

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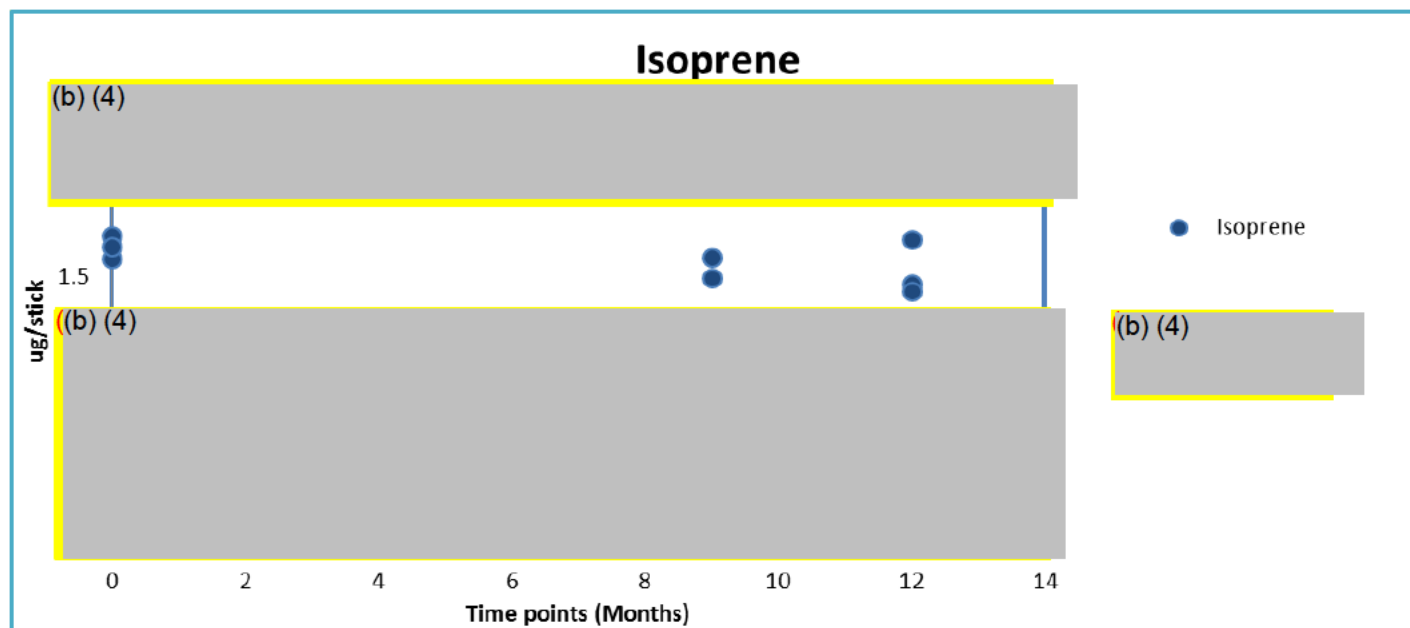Form Status: Effective
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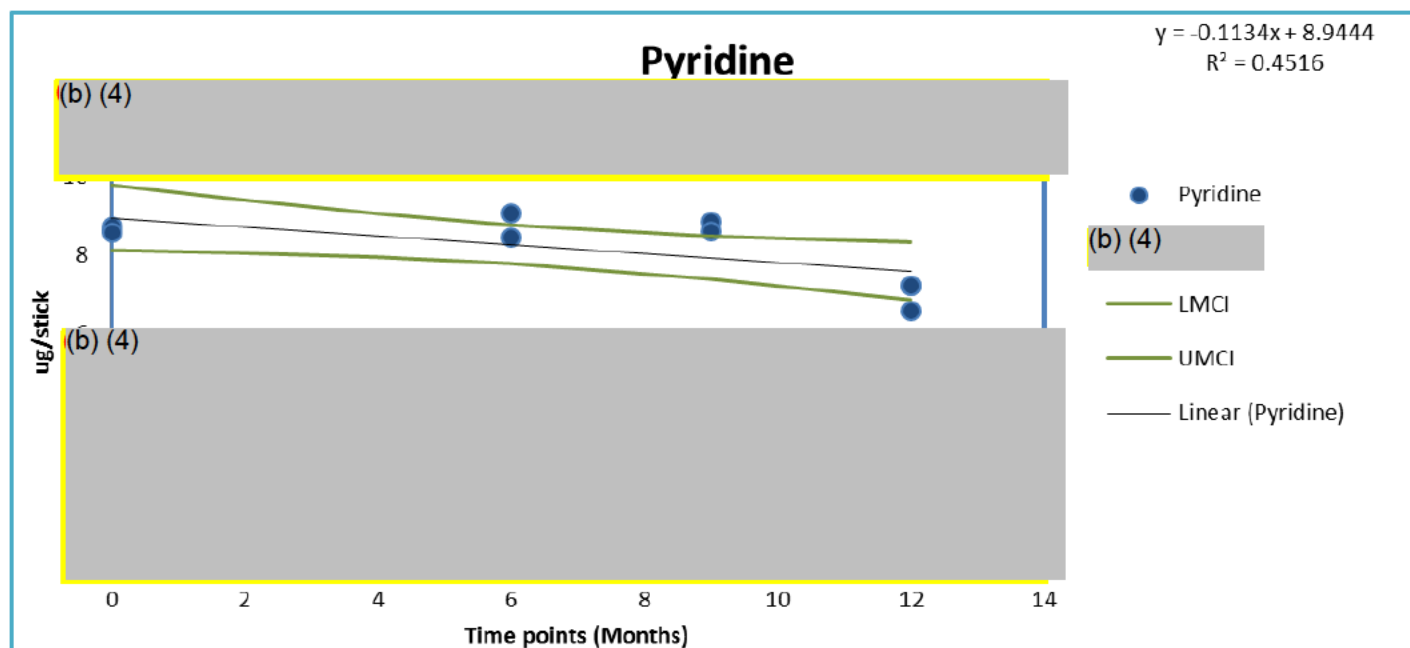
6.1.1.12 Acrylonitrile

Figure 12 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.

6.1.1.13 Isoprene

Figure 13 There is no obvious change over time in Isoprene level and all the values are well inside the specifications, therefore Isoprene is considered stable for 12 months.

6.1.1.14 Pyridine
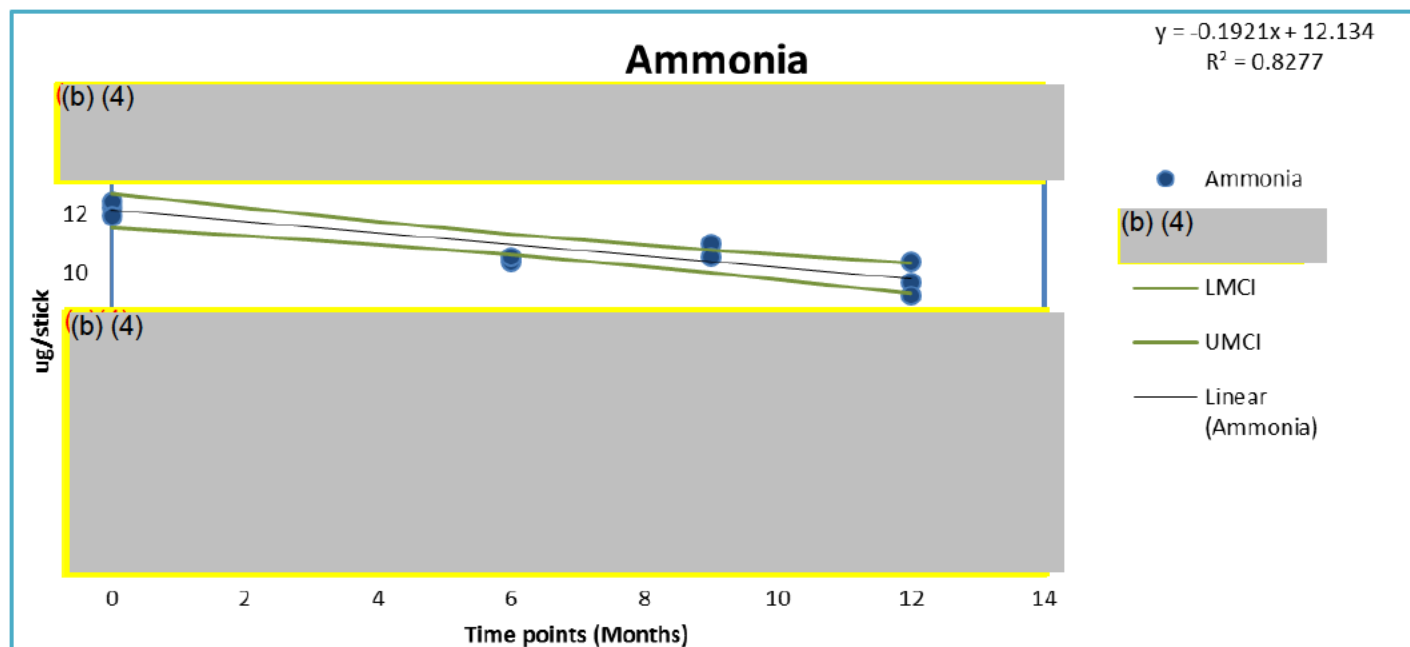

Figure 14 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.

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6.1.1.15 Ammonia

Figure 15 The best model accepted at the significance level of 0.25 has Different intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.

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6.1.2 Physical Attributes Evaluation

(b) (4)

6.1.3 Sensorial Evaluation

Sensorial evaluation results are described in details in a separate report [5].

No drastic sensory changes were observed over the storage time of 12 months at condition 22°C 60%RH. (b) (4)
(b) (4)   Based on the 12 months evaluation it is
hypothesized that consumers should not reject the product for a period up to 12 month storage in 22°C 60% RH.

Therefore, a shelf life of 12 months could is considered as acceptable.

6.1.4 Visual inspection

The visual quality of the tobacco sticks was found acceptable from visual point of view after 12 months of storage in 22°C 60%RH.

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6.2 Storage Condition 30°C 35% RH

Table 8 B-25900 / 41.2381531 at 30°C 35% RH

B-25900 / 41.2381531	Unit	Specifications		Time point (Months)						Degradation Rate	R^2	Severity Score
Test		Lower	Upper	0	2	4	6	9	12			
Menthol	mg/stick	(b) (4)		1.25	1.85		1.68	1.74	1.70	1.49%	0.23	0.3
Nicotine	mg/stick			1.17	1.14		1.12	1.09	1.07	-0.70%	0.98	0.7
Glycerin	mg/stick			4.68	4.74		4.49	4.35	3.99	-1.20%	0.90	1.1
CO	mg/stick			0.3	0.3		0.4	0.5	0.3	2.25%	0.17	0.4
Triacetin	mg/stick			0.5	0.5		0.4	0.4	0.4	-1.94%	0.85	1.6
Phenol	µg/stick			1.2	1.3		1.4	1.2	1.1	-0.42%	0.04	0.0
Acrylamide	µg/stick			1.4	1.4		1.5	1.3	1.2	-1.17%	0.45	0.5
Acetamide	µg/stick			3.0			2.9	2.7	2.7	-1.00%	0.87	0.9
Acetaldehyde	µg/stick			205			189	194	197	-0.34%	0.26	0.1
Butyraldehyde	µg/stick			13.9			11.7	12.4	11.3	-1.40%	0.78	1.1
Acrylonitrile	µg/stick			0.16	0.15		0.14	0.13	0.13	-1.70%	0.88	1.5
Isoprene	µg/stick			1.59				1.48	1.32	-1.27%	0.85	1.1
Pyridine	µg/stick			8.6			8.4	8.8	8.3	-0.18%	0.14	0.0
Ammonia	µg/stick			12.3			7.9	8.0	6.8	-3.82%	0.89	3.4
TPM	mg/stick			54	53		52	51	48	-0.88%	0.94	0.8

(b) (4)

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Table 9 B-25901 / 41.2374718 at 30°C 35% RH

B-25901 / 41.2374718	Unit	Specifications		Time point (Months)						Degradation Rate	R^2	Severity Score
Test		Lower	Upper	0	2	4	6	9	12			
Menthol	mg/stick	(b) (4)		1.23		2.00	1.97		1.66	1.75%	0.15	0.3
Nicotine	mg/stick			1.23		1.13	1.22		1.15	-0.41%	0.26	0.1
Glycerin	mg/stick			4.53		4.36	4.50		4.17	-0.60%	0.72	0.4
CO	mg/stick			0.3		0.5	0.4		0.3	-0.81%	0.03	0.0
Triacetin	mg/stick			0.5		0.4	0.5		0.4	-1.33%	0.52	0.7
Phenol	µg/stick			1.2		1.6	1.4		1.1	-1.01%	0.12	0.1
Acrylamide	µg/stick			1.4		1.4	1.6		1.3	-0.63%	0.12	0.1
Acetamide	µg/stick			3.2			3.1		2.9	-0.87%	1.00	0.9
Acetaldehyde	µg/stick			195			196		207	0.52%	0.80	0.4
Butyraldehyde	µg/stick			13.4			12.0		11.9	-0.98%	0.83	0.8
Acrylonitrile	µg/stick			0.17		0.16	0.14		0.14	-1.35%	0.80	1.1
Isoprene	µg/stick			1.72					1.39	NA	NA	NA
Pyridine	µg/stick			8.7			8.6		8.5	-0.25%	0.97	0.2
Ammonia	µg/stick			12.5			8.2		6.9	-3.84%	0.91	3.5
TPM	mg/stick			56	52	52		50		-0.88%	0.82	0.7

(b) (4)

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Table 10 B-25902 / 41.2379112 at 30°C 35% RH

B-25902 / 41.2379112	Unit	Specifications		Time point (Months)						Degradation Rate	R^2	Severity Score
Test		Lower	Upper	0	2	4	6	9	12			
Menthol	mg/stick	(b) (4)		1.05	1.67	1.68		1.65	1.60	2.02%	0.27	0.5
Nicotine	mg/stick			1.22	1.14	1.11	1.11	1.10	1.10	-0.68%	0.64	0.4
Glycerin	mg/stick			4.59	4.66	3.66	4.13	4.13	3.78	-1.34%	0.43	0.6
CO	mg/stick			0.3	0.3	0.5	0.4	0.4	0.3	0.34%	0.00	0.0
Triacetin	mg/stick			0.5	0.4	0.4	0.4	0.4	0.4	-1.70%	0.63	1.1
Phenol	µg/stick			1.3	1.2	1.1	1.1	1.0	0.9	-2.55%	0.97	2.5
Acrylamide	µg/stick			1.4	1.3	1.2	1.4	1.2	1.1	-1.52%	0.60	0.9
Acetamide	µg/stick			3.0				2.8	2.7	-0.88%	0.97	0.9
Acetaldehyde	µg/stick			195				189	206	0.26%	0.13	0.0
Butyraldehyde	µg/stick			13.4				11.9	11.9	-1.02%	0.94	1.0
Acrylonitrile	µg/stick			0.16	0.15	0.15		0.13	0.14	-1.14%	0.63	0.7
Isoprene	µg/stick			1.66				1.48	1.37	-1.39%	0.98	1.4
Pyridine	µg/stick			8.6				8.9	8.4	-0.05%	0.01	0.0
Ammonia	µg/stick			12.0				7.6	6.2	-4.04%	1.00	4.0
TPM	mg/stick			56	54	49	51	51	48	-0.98%	0.68	0.7

(b) (4)

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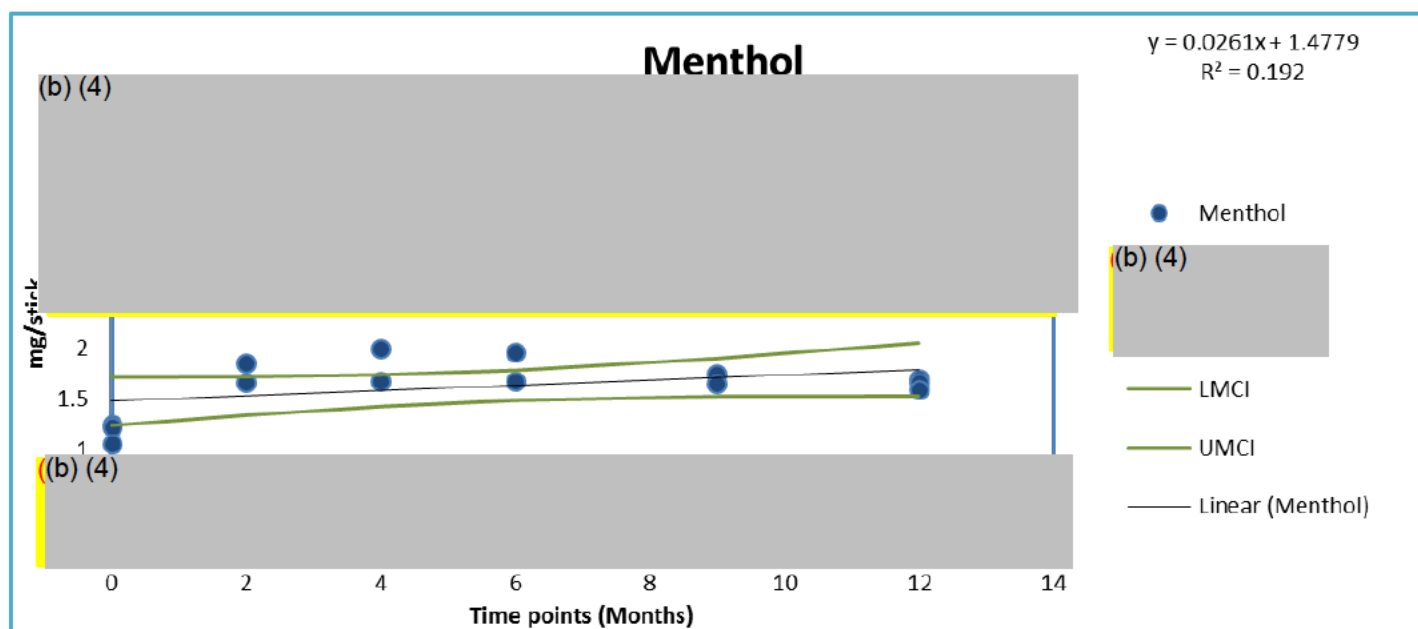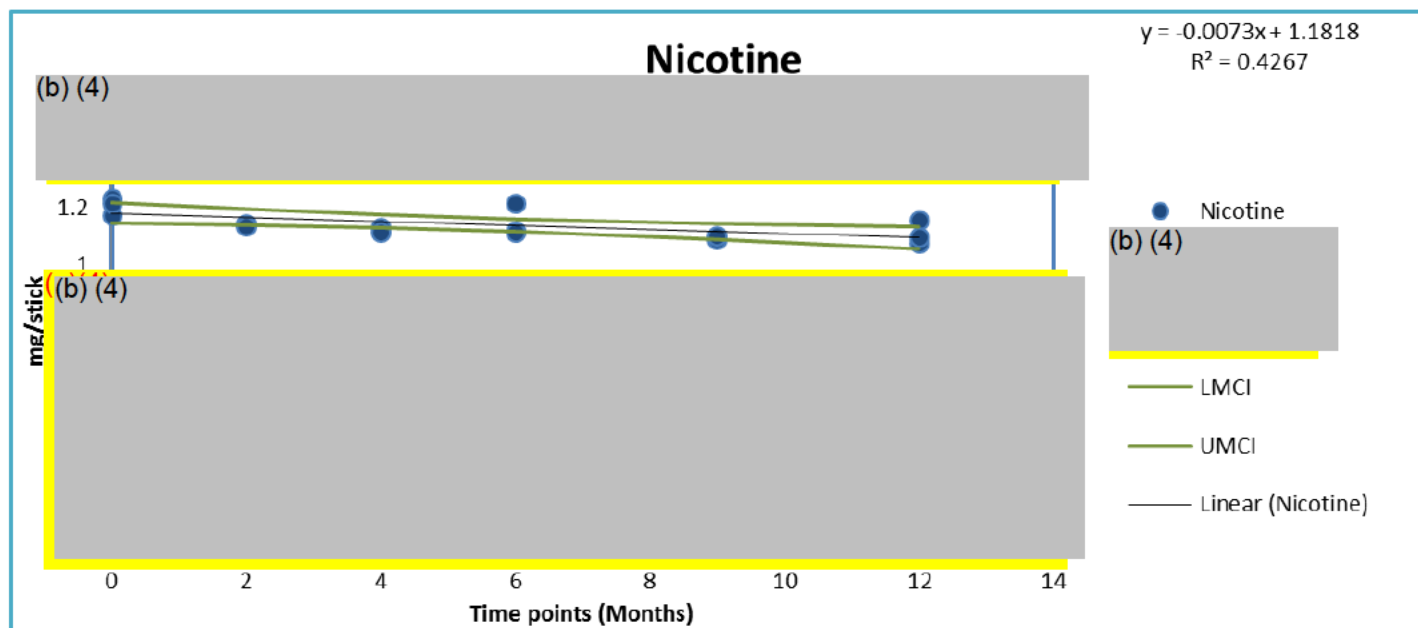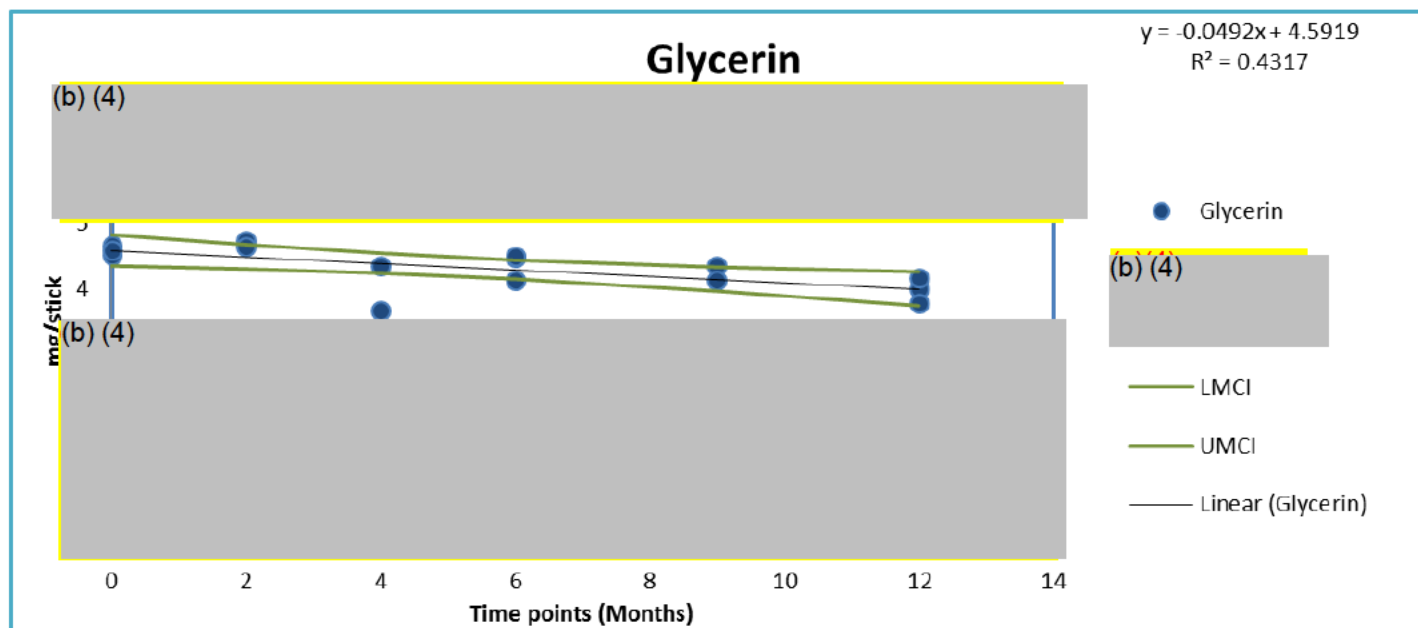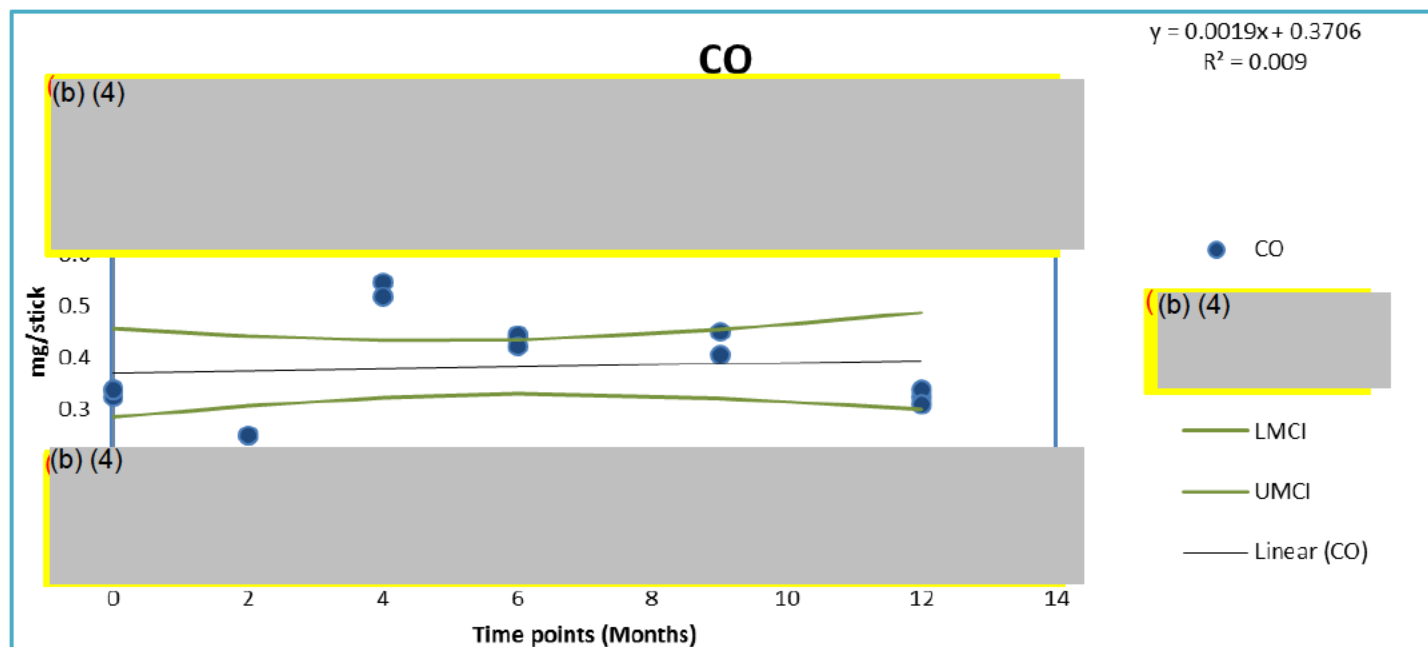### 6.2.1 Mainstream Aerosol Evaluation

6.2.1.1 Menthol

Figure 17 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.

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6.2.1.2 Nicotine

Figure 18 The best model accepted at the significance level of 0.25 has Different intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.
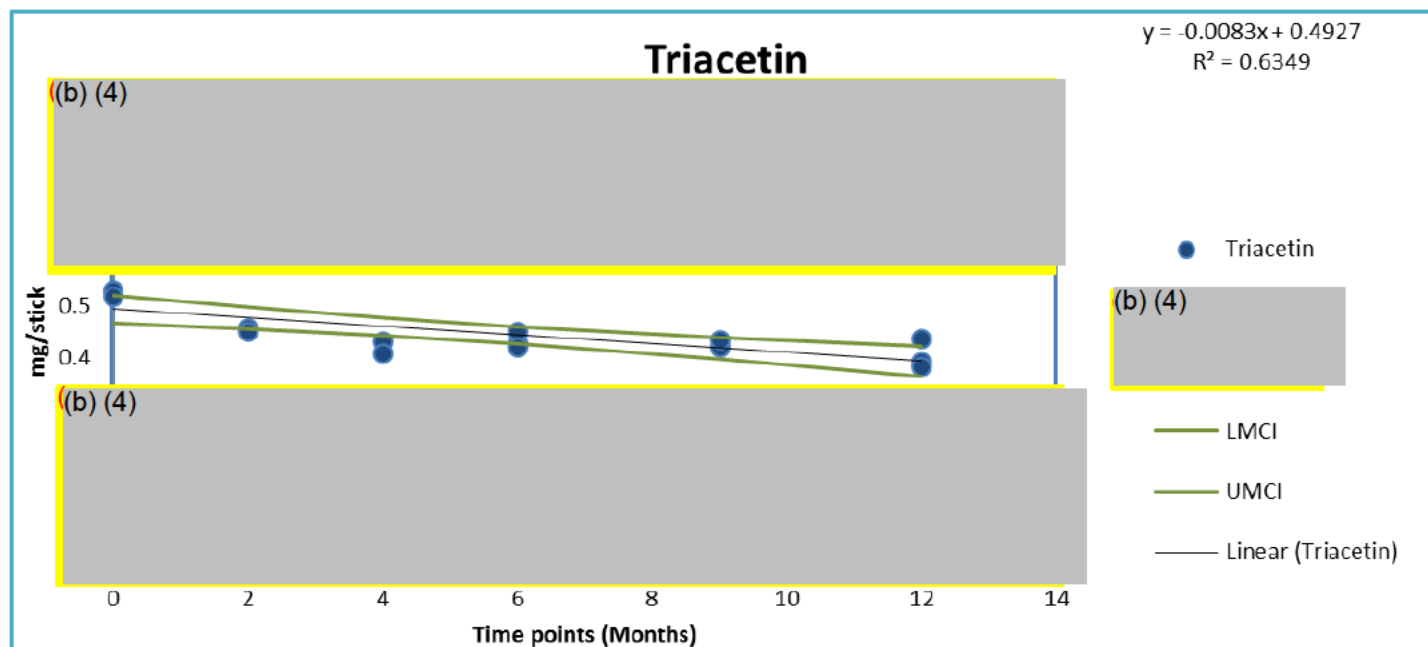
6.2.1.3 Glycerin

Figure 19 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.

6.2.1.4 CO

Figure 20 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.
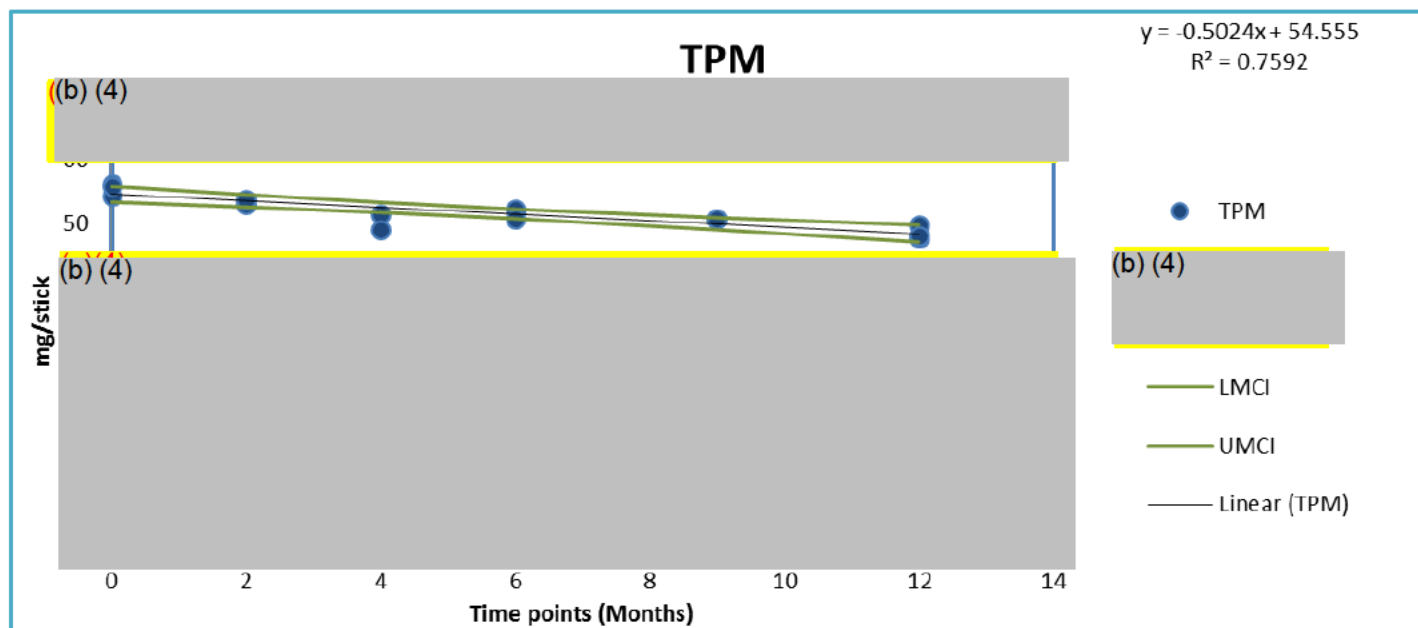
6.2.1.5 Triacetin

Figure 21 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.

6.2.1.6 TPM

Figure 22 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.

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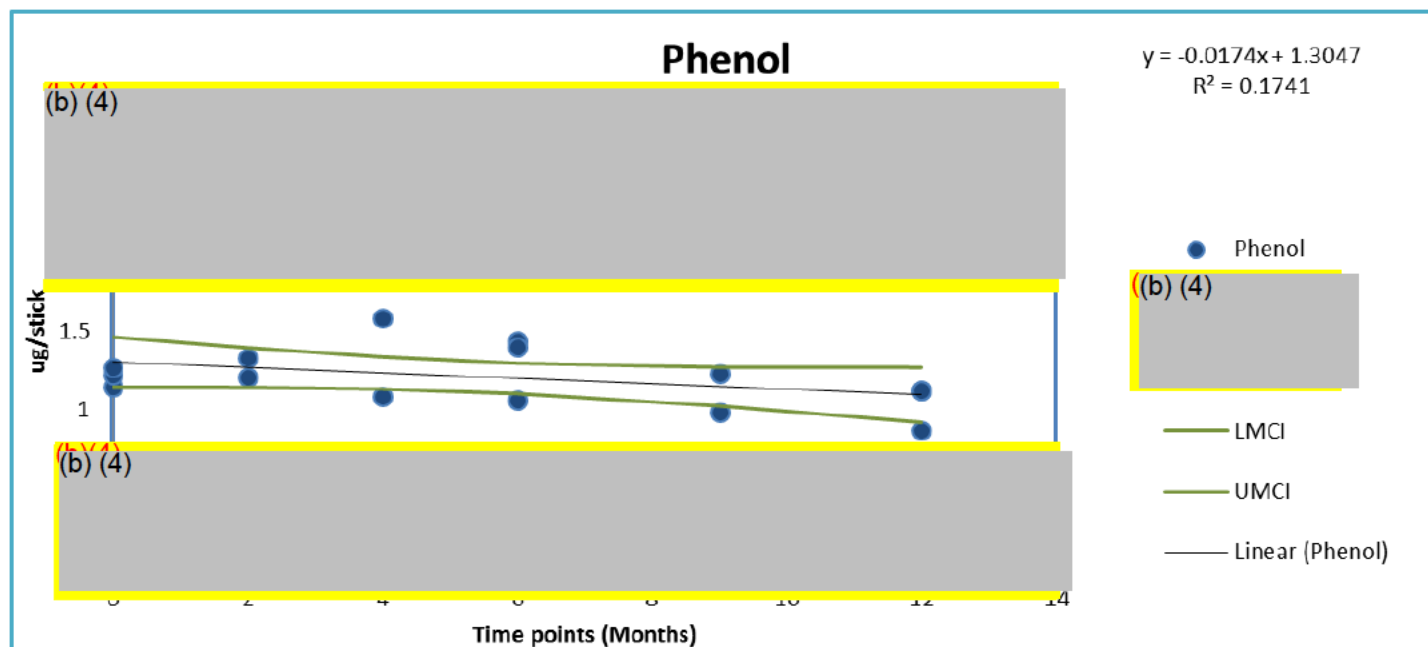
6.2.1.7 Phenol

Figure 23 The best model accepted at the significance level of 0.25 has Different intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.
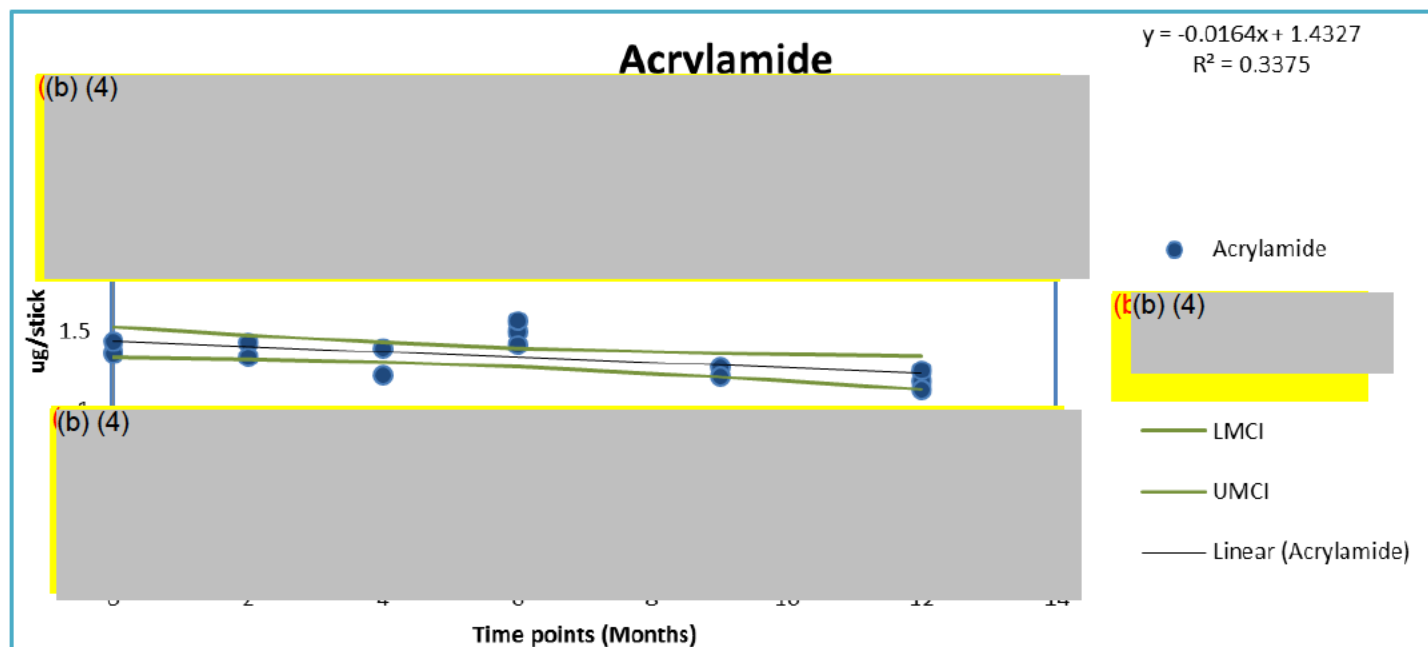
6.2.1.8 Acrylamide

Figure 24 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.

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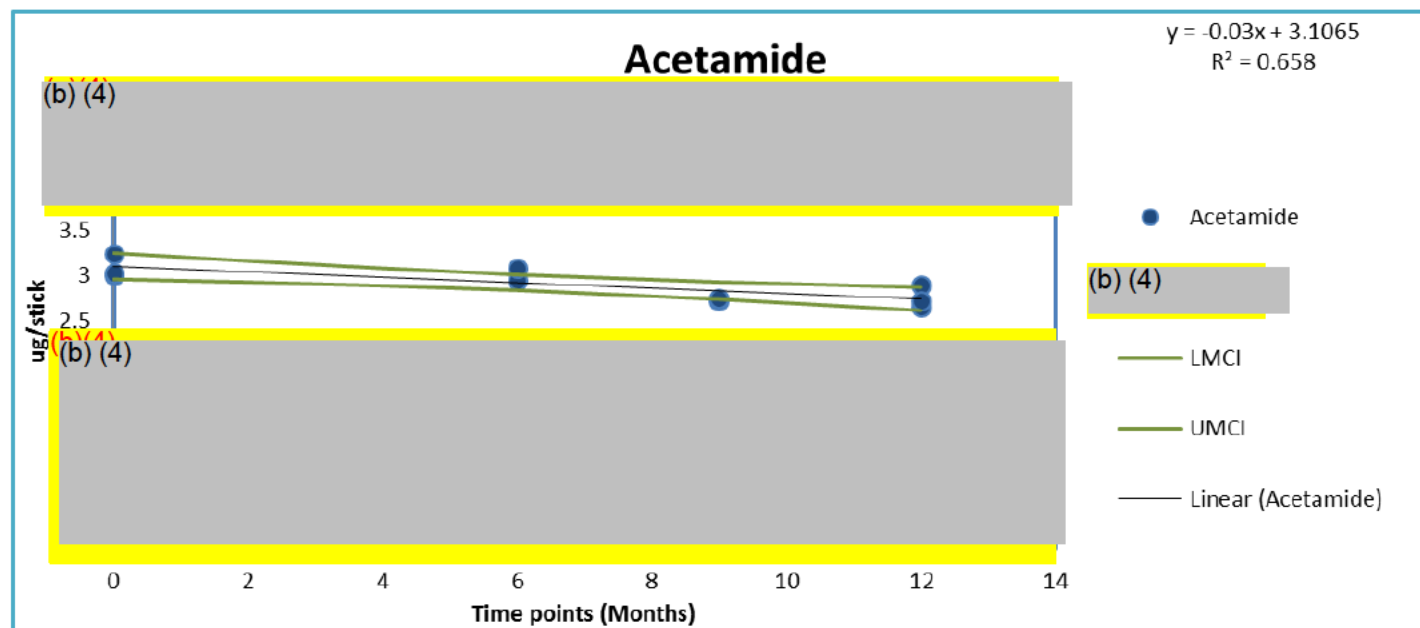
6.2.1.9 Acetamide

Figure 25 The best model accepted at the significance level of 0.25 has Different intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.

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6.2.1.10 Acetaldehyde

$y = 0.2255x + 195.78$
$R^2 = 0.0286$

Acetaldehyde

(b) (4)

(b) (4)

(b) (4)

● Acetaldehyde

—— LMCI

—— UMCI

—— Linear (Acetaldehyde)
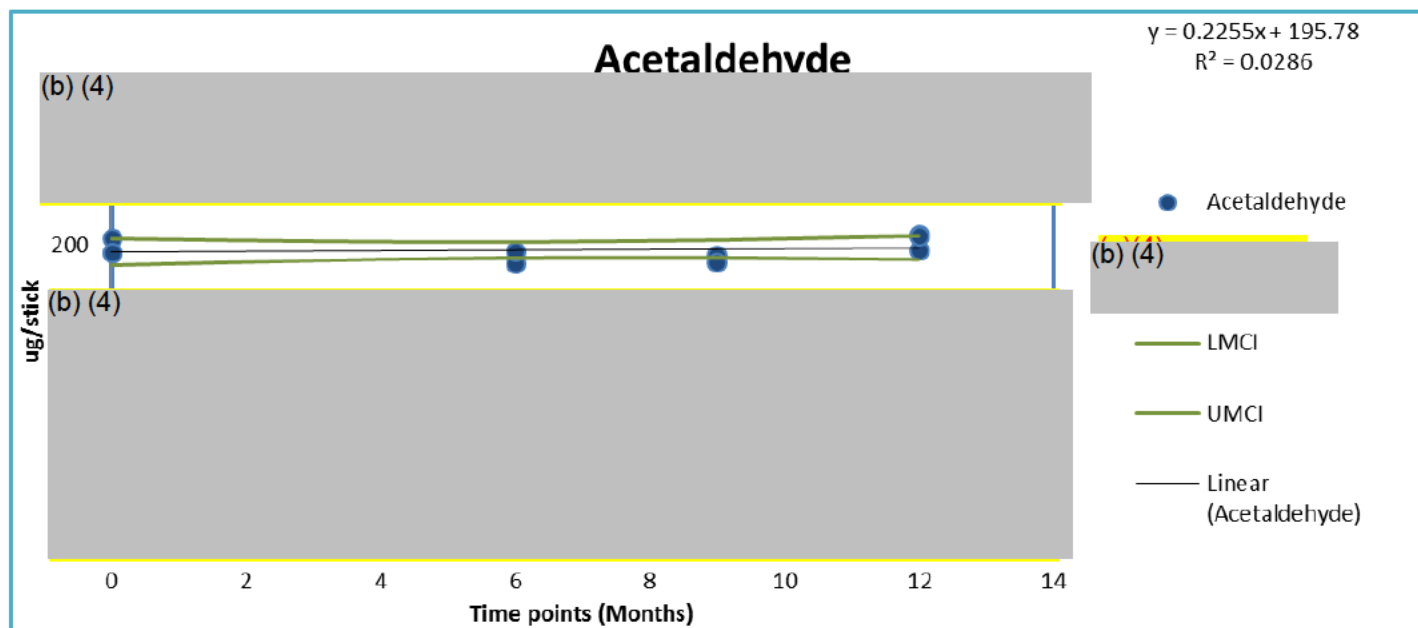
ug/stick

Time points (Months)

Figure 26 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.
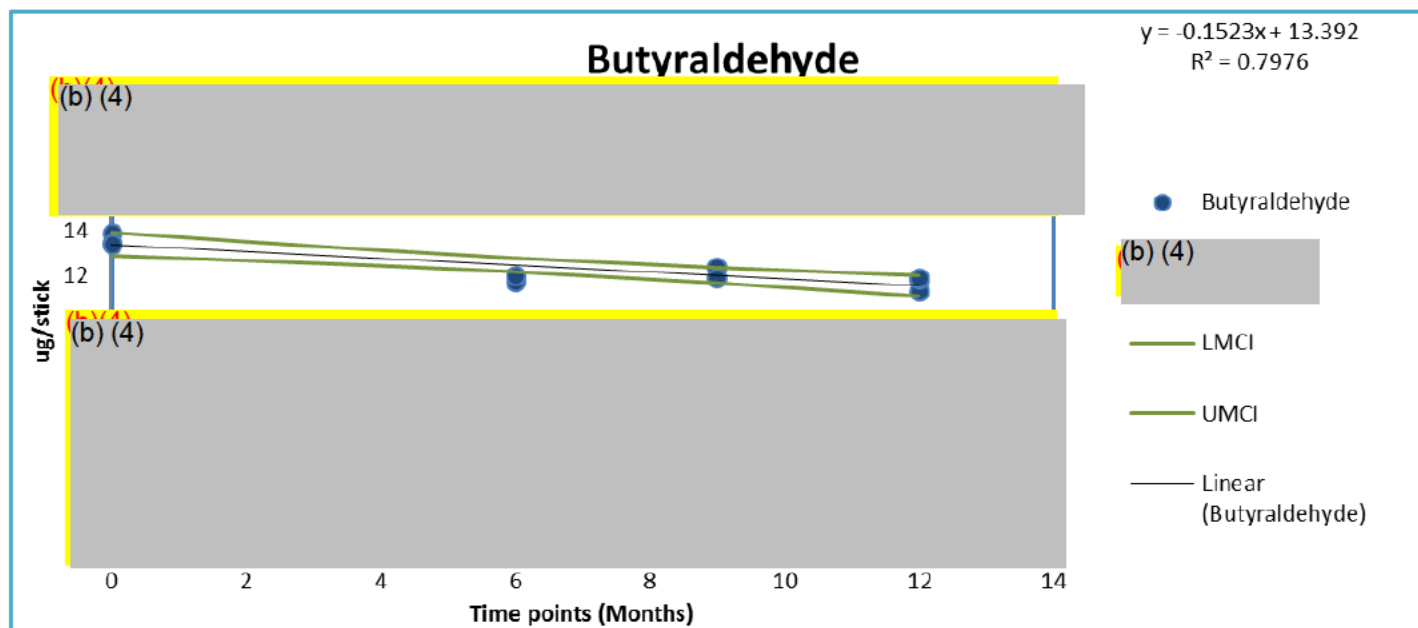
6.2.1.11 Butyraldehyde

Figure 27 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.

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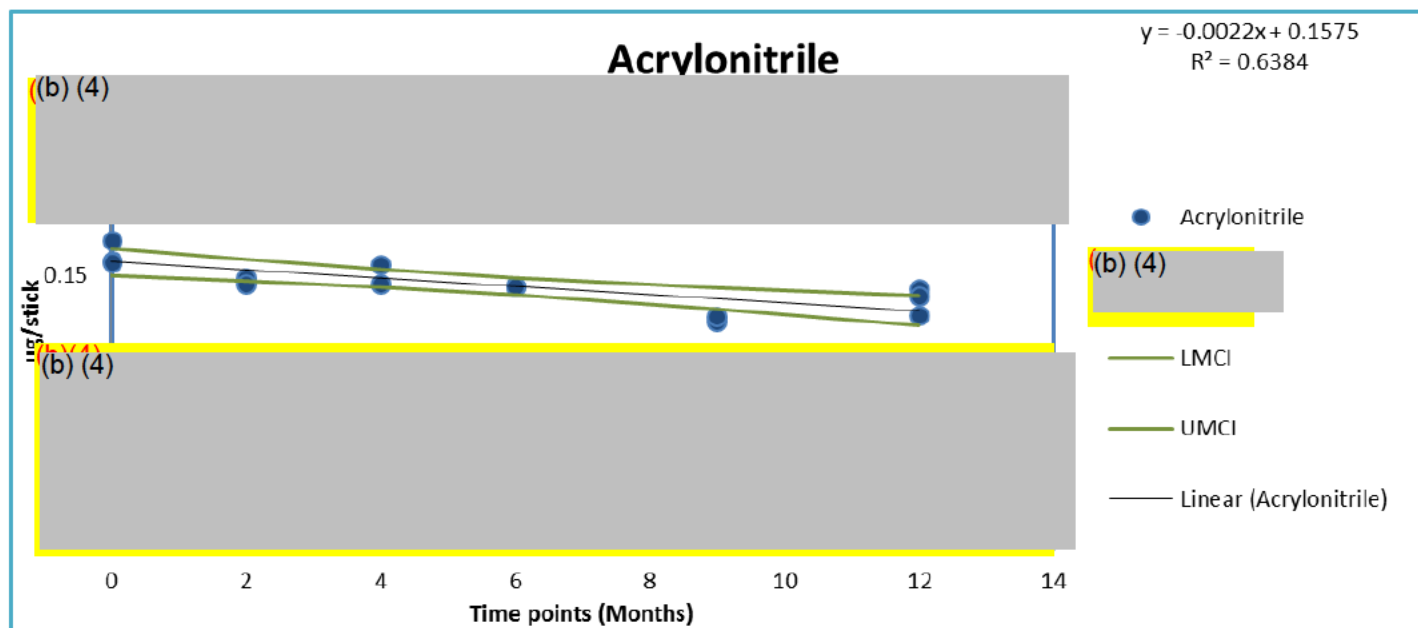
6.2.1.12 Acrylonitrile

Figure 28 The best model accepted at the significance level of 0.25 has Different intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.
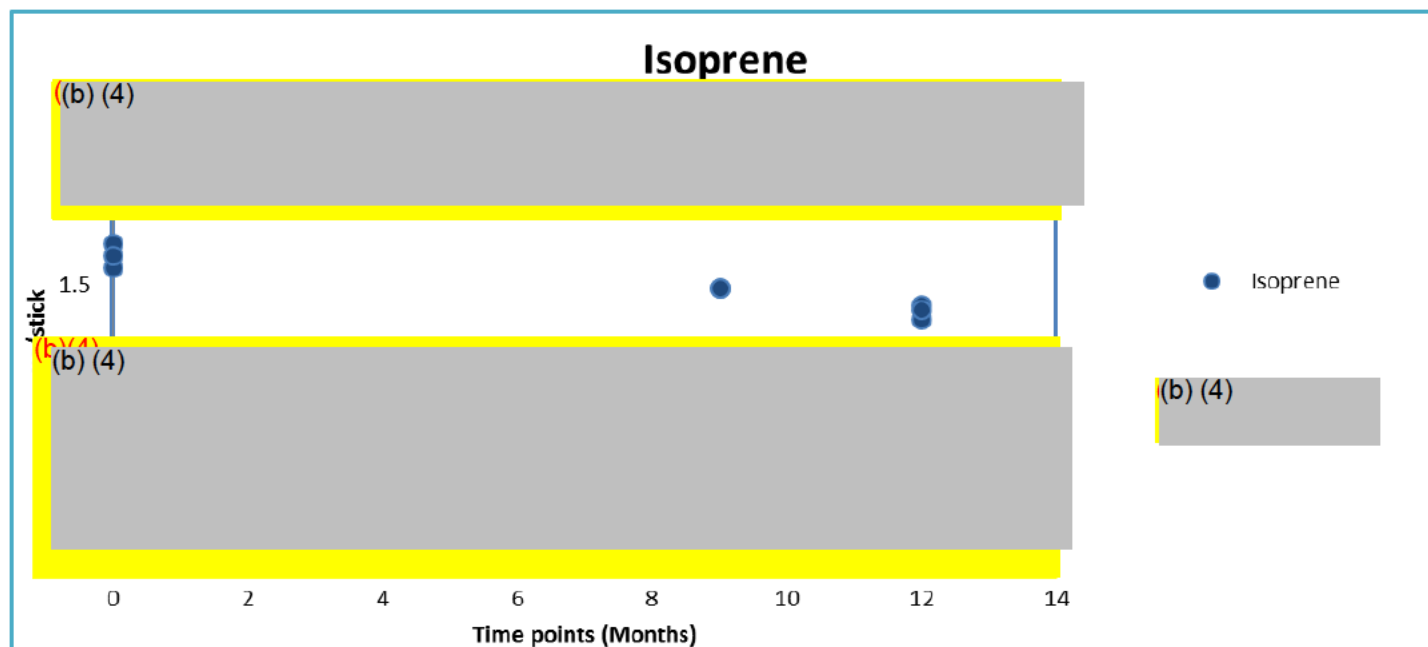
6.2.1.13 Isoprene

Figure 29 There is no obvious change over time in Isoprene level and all the values are well inside the specifications, therefore Isoprene is considered stable for 12 months.

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6.2.1.14 Pyridine

Figure 30 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.
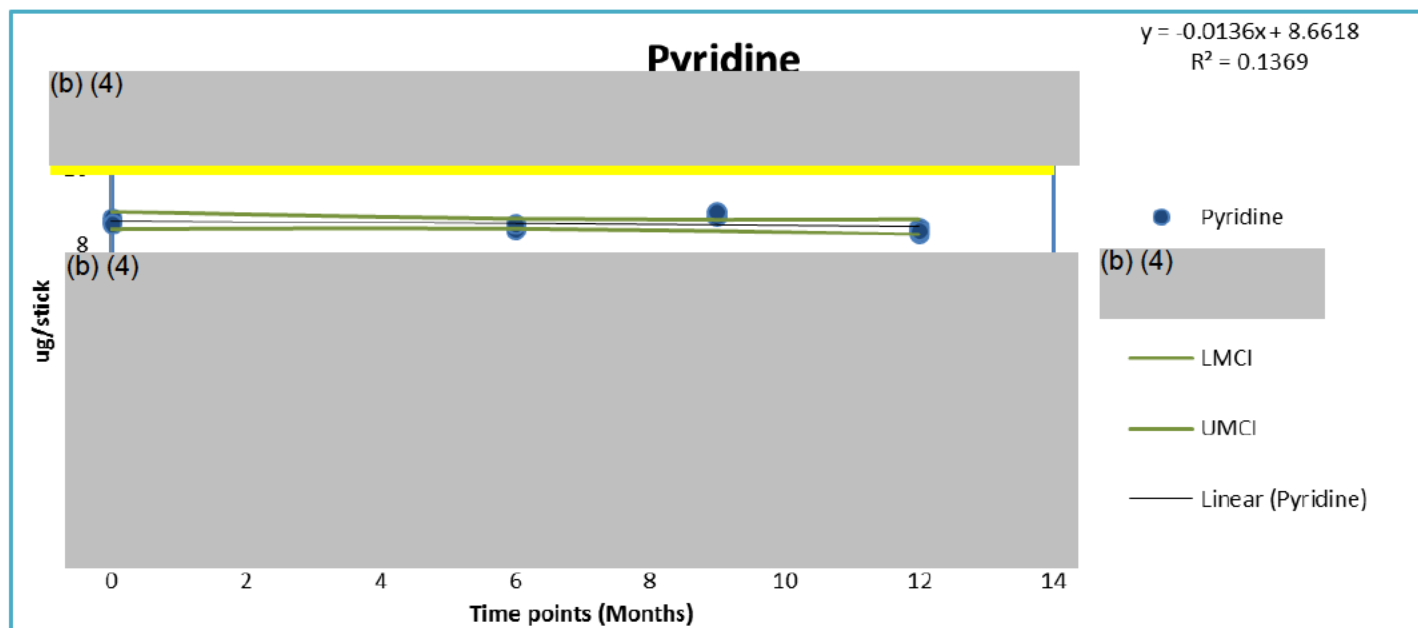
6.2.1.15 Ammonia

Figure 31 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.

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6.2.2 Physical Attributes Evaluation

(b) (4)

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6.2.3 Sensorial Evaluation

Sensorial evaluation results are described in details in a separate report [5].

No drastic sensory changes were observed over the storage time of 12 months at condition 30°C 35%RH. (b) (4)
(b) (4)   Based on the 12 months evaluation it
is hypothesized that consumers should not reject the product for a period up to 12 month storage in 30⁰C 35% RH.

Therefore, a shelf life of 12 months could is considered as acceptable.

6.2.4 Visual inspection

The visual quality of the tobacco sticks was found acceptable from visual point of view after 12 months of storage in 30⁰C 35%RH.

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6.3 Storage Condition 30⁰C 75% RH

Table 11 B-25900 / 41.2381531 at 30⁰C 75% RH

B-25900 / 41.2381531	Unit	Specifications		Time point (Months)						Degradation Rate	R^2	Severity Score
Test		Lower	Upper	0	2	4	6	9	12			
Menthol	mg/stick	(b) (4)		1.25	1.88	1.73				8.74%	0.53	4.6
Nicotine	mg/stick			1.17	1.15	1.06				-2.37%	0.91	2.2
Glycerin	mg/stick			4.68	4.67	4.02				-3.46%	0.76	2.6
CO	mg/stick			0.3	0.3	0.5				18.04%	0.56	10.1
Triacetin	mg/stick			0.5	0.4	0.3				-9.28%	0.97	9.0
Phenol	µg/stick			1.2	1.3	1.3				3.93%	0.87	3.4
Acrylamide	µg/stick			1.4	1.4	1.3				-1.91%	0.80	1.5
Acetamide	µg/stick			3.0						NA	NA	NA
Acetaldehyde	µg/stick			205						NA	NA	NA
Butyraldehyde	µg/stick			13.9						NA	NA	NA
Acrylonitrile	µg/stick			0.16	0.14	0.16				-0.36%	0.01	0.0
Isoprene	µg/stick			1.59	1.64*	1.86*				NA	NA	NA
Pyridine	µg/stick			8.6						NA	NA	NA
Ammonia	µg/stick			12.3						NA	NA	NA
TPM	mg/stick			54	53	50				-1.78%	0.96	1.7

(b) (4)

* Isoprene values in T2 and T4 ar   explained in Chapter 5.2.

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Table 12 B-25901 / 41.2374718 at 30^0C 75% RH

B-25901 / 41.2374718	Unit	Specifications		Time point (Months)						Degradation Rate	R^2	Severity Score
Test		Lower	Upper	0	2	4	6	9	12			
Menthol	mg/stick	(b) (4)		1.23	1.86		1.88			6.71%	0.60	4.0
Nicotine	mg/stick			1.23	1.17		1.19			-0.39%	0.21	0.1
Glycerin	mg/stick			4.53	4.79		4.33			-0.96%	0.35	0.3
CO	mg/stick			0.3	0.3		0.5			10.39%	0.57	5.9
Triacetin	mg/stick			0.5	0.5		0.4			-4.50%	0.97	4.4
Phenol	µg/stick			1.2	1.7		1.6			3.26%	0.35	1.1
Acrylamide	µg/stick			1.4	1.4		1.6			2.42%	1.00	2.4
Acetamide	µg/stick			3.2			3.2			NA	NA	NA
Acetaldehyde	µg/stick			195			212			NA	NA	NA
Butyraldehyde	µg/stick			13.4			12.2			NA	NA	NA
Acrylonitrile	µg/stick			0.17	0.14		0.17			0.26%	0.01	0.0
Isoprene	µg/stick			1.72	1.66*		2.30*			NA	NA	NA
Pyridine	µg/stick			8.7			8.6			NA	NA	NA
Ammonia	µg/stick			12.5			8.9			NA	NA	NA
TPM	mg/stick			56	54		54			-0.60%	0.54	0.3

(b) (4)

* Isoprene values in T2 and T4 ar[...]xplained in Chapter 5.2.

Table 13 B-25902 / 41.2379112 at 30°C 75% RH

B-25902 / 41.2379112	Unit	Specifications		Time point (Months)						Degradation Rate	R^2	Severity Score
Test		Lower	Upper	0	2	4	6	9	12			
Menthol	mg/stick	(b) (4)		1.05		1.85	1.93			13.95%	0.94	13.1
Nicotine	mg/stick			1.22		1.07	1.19			-0.73%	0.12	0.1
Glycerin	mg/stick			4.59		4.04	4.41			-1.00%	0.24	0.2
CO	mg/stick			0.3		0.5	0.5			6.88%	0.55	3.8
Triacetin	mg/stick			0.5		0.4	0.4			-5.09%	0.78	4.0
Phenol	µg/stick			1.3		1.1	1.5			2.47%	0.18	0.4
Acrylamide	µg/stick			1.4		1.3	1.6			1.20%	0.10	0.1
Acetamide	µg/stick			3.0			3.3			NA	NA	NA
Acetaldehyde	µg/stick			195			229			NA	NA	NA
Butyraldehyde	µg/stick			13.4			13.7			NA	NA	NA
Acrylonitrile	µg/stick			0.16		0.13	0.14			-1.96%	0.61	1.2
Isoprene	µg/stick			1.66		1.56*	1.82*			NA	NA	NA
Pyridine	µg/stick			8.6			8.2			NA	NA	NA
Ammonia	µg/stick			12.0			8.7			NA	NA	NA
TPM	mg/stick			56		51	53			-1.07%	0.58	0.6

(b) (4)

6.3.1 Mainstream Aerosol Evaluation

6.3.1.1 Menthol

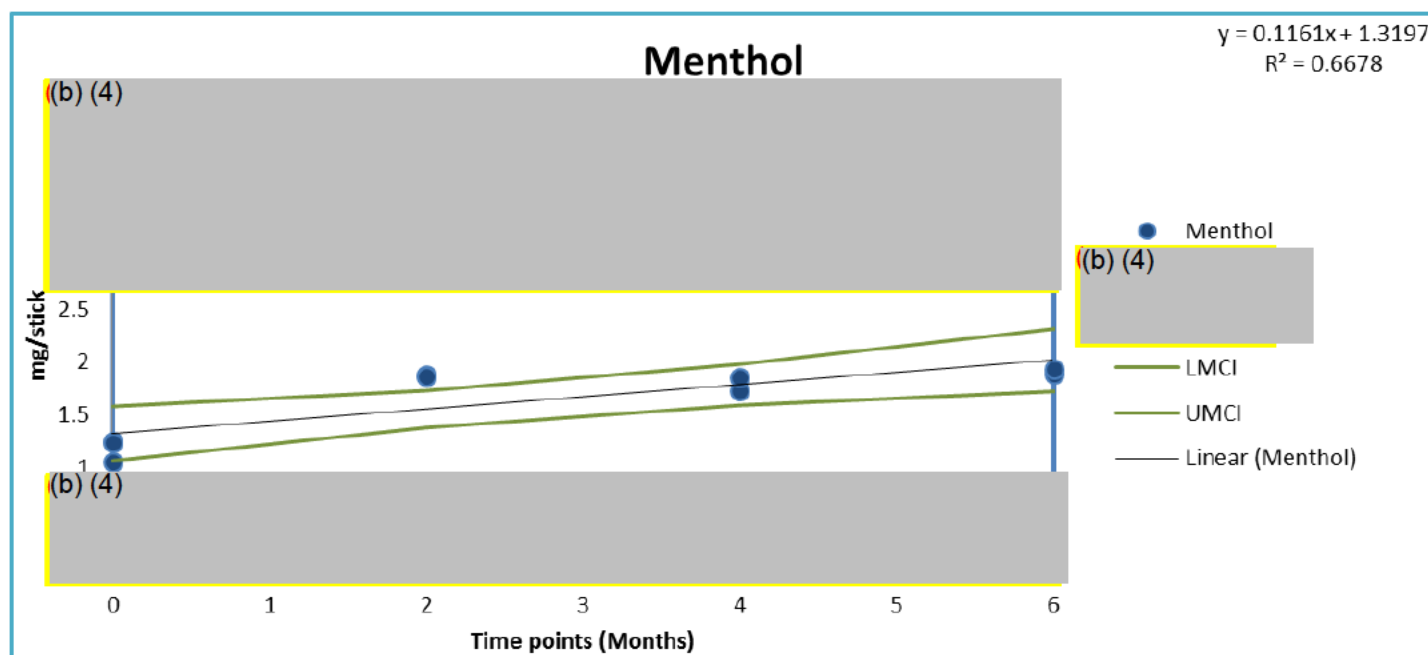
$$y = 0.1161x + 1.3197$$
$$R^2 = 0.6678$$

Figure 33 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 6 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 6 months.
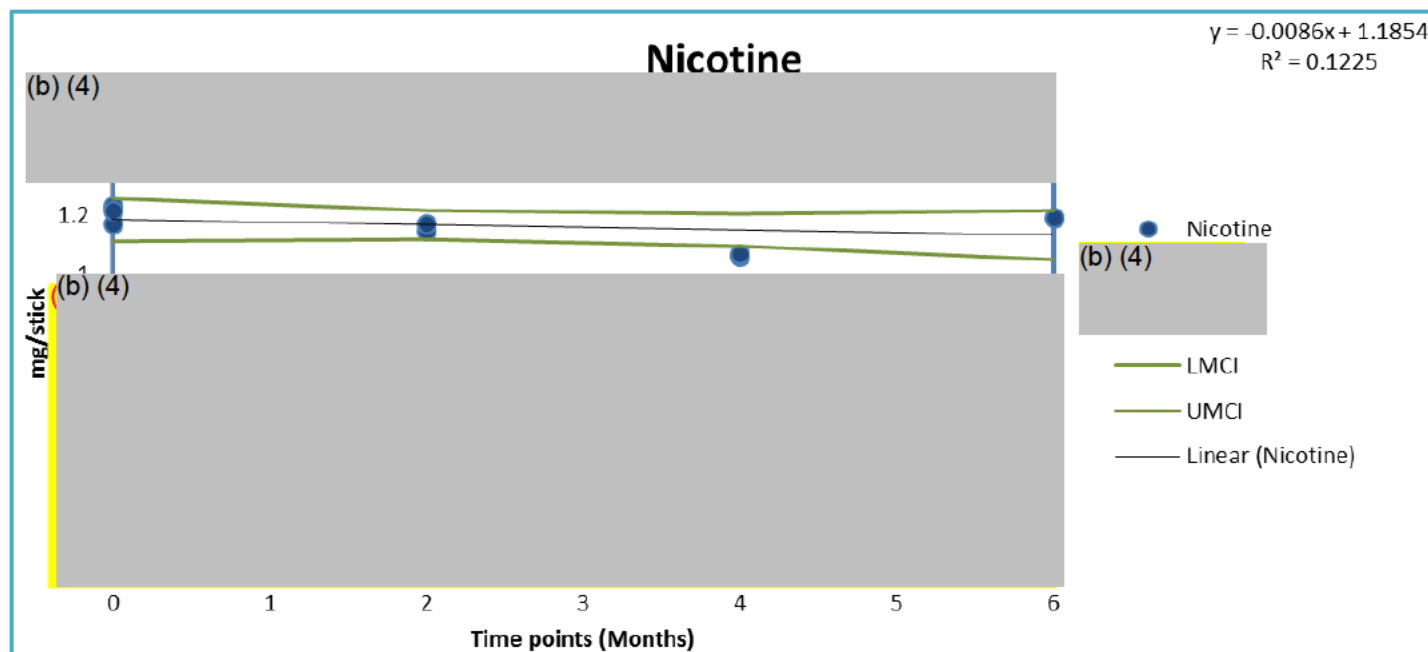
6.3.1.2 Nicotine

Figure 34 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 6 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 6 months.

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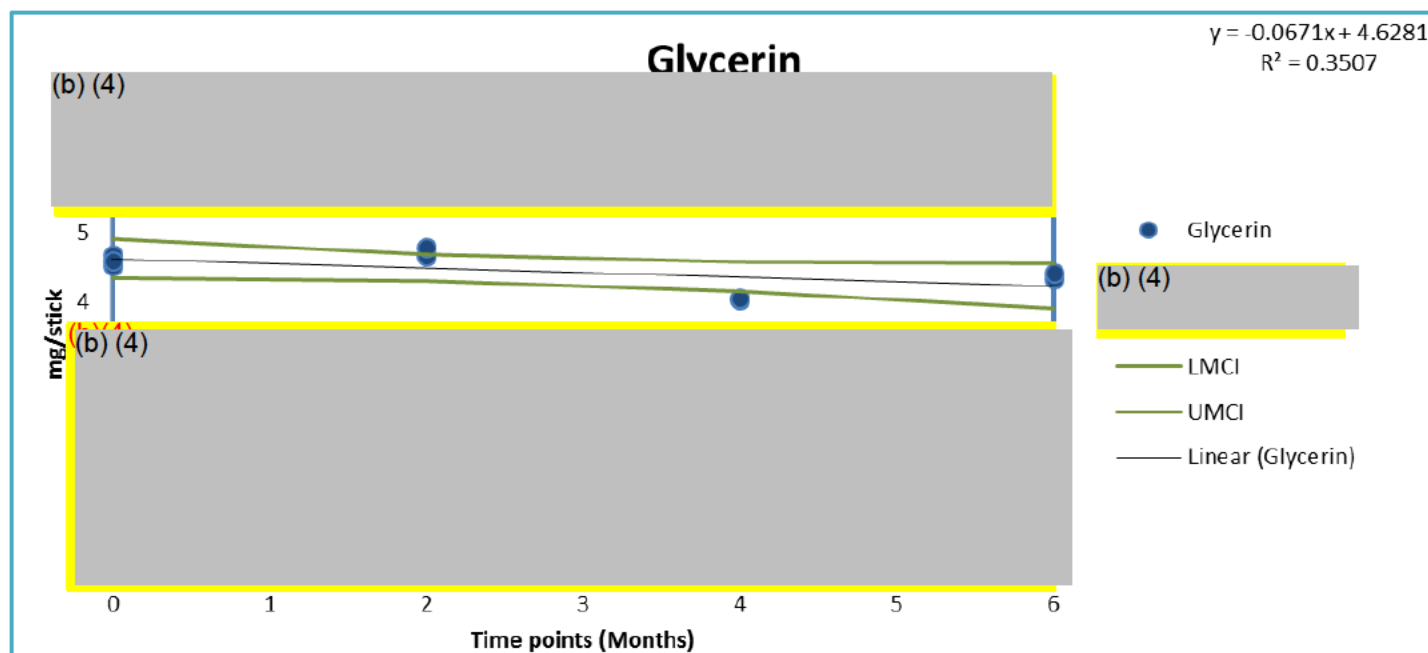
6.3.1.3 Glycerin

Figure 35 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 6 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 6 months.

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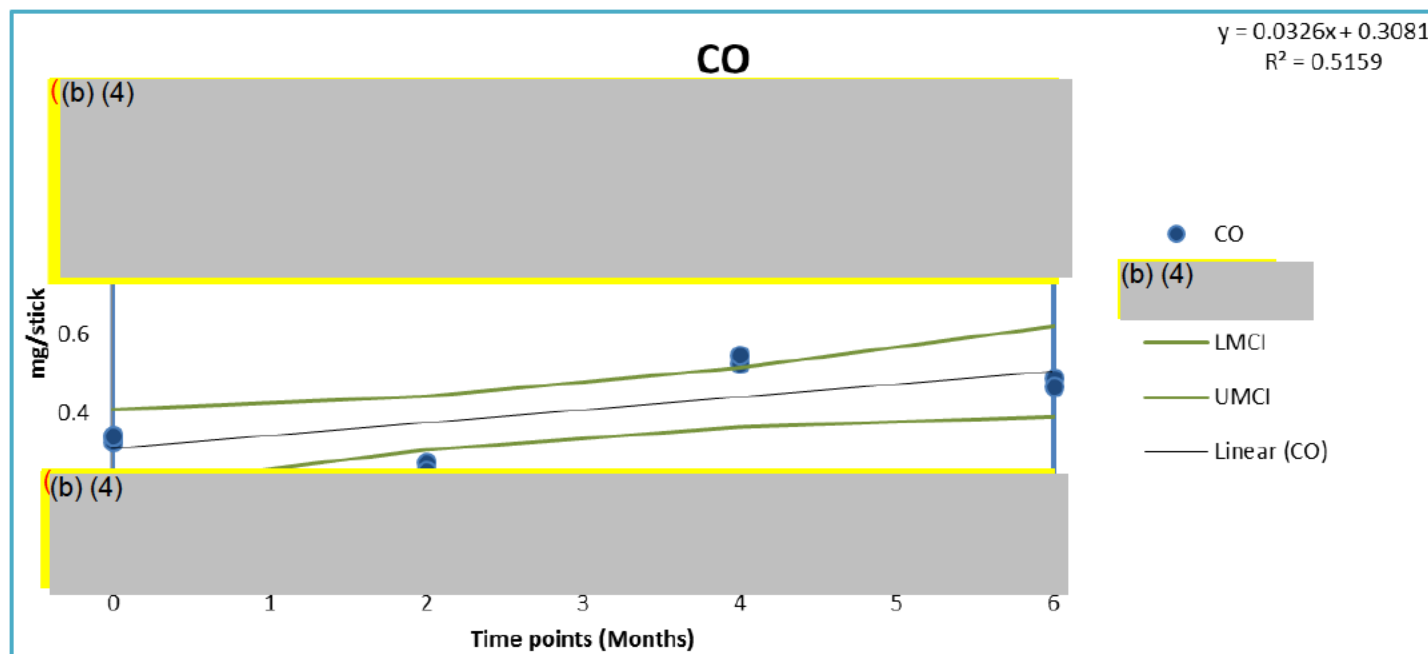| Form Number: PMI_RD_FOR_000927	Form Version N°: 1.0	Form Status: Effective
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6.3.1.4 CO

Figure 36 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 6 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 6 months.
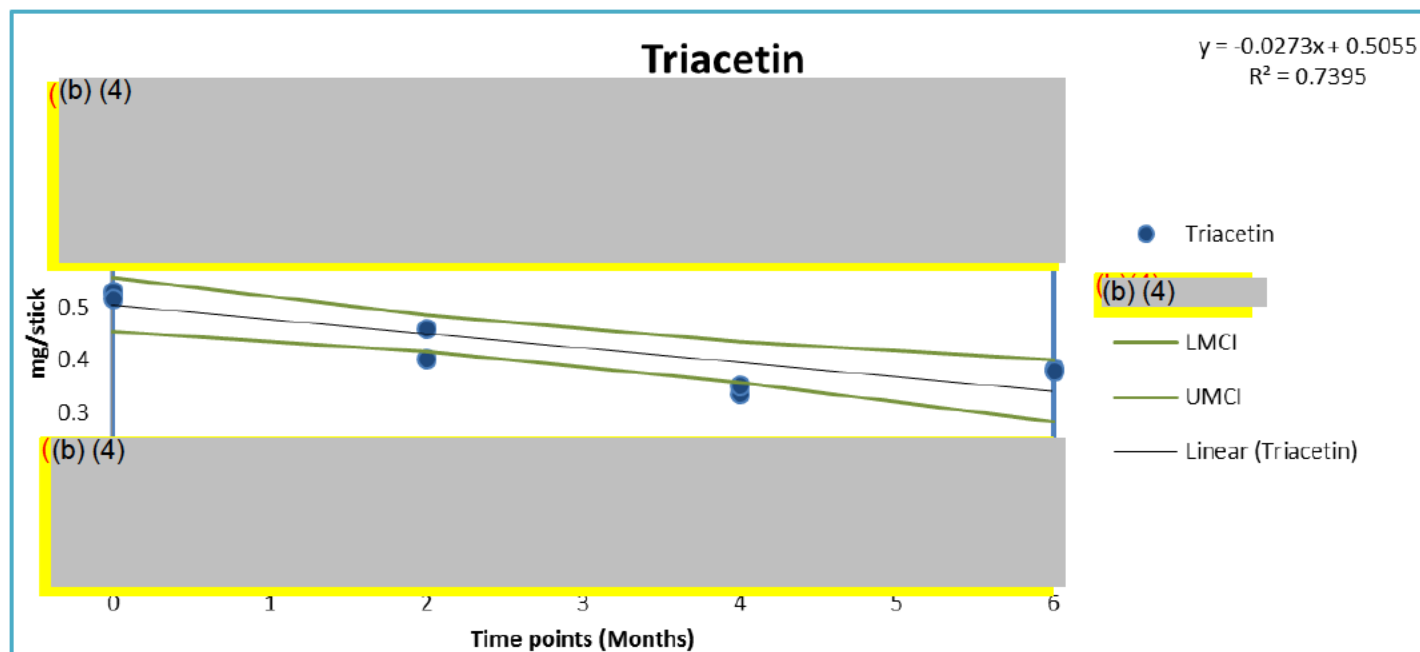
6.3.1.5 Triacetin

Figure 37 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 6 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 6 months.

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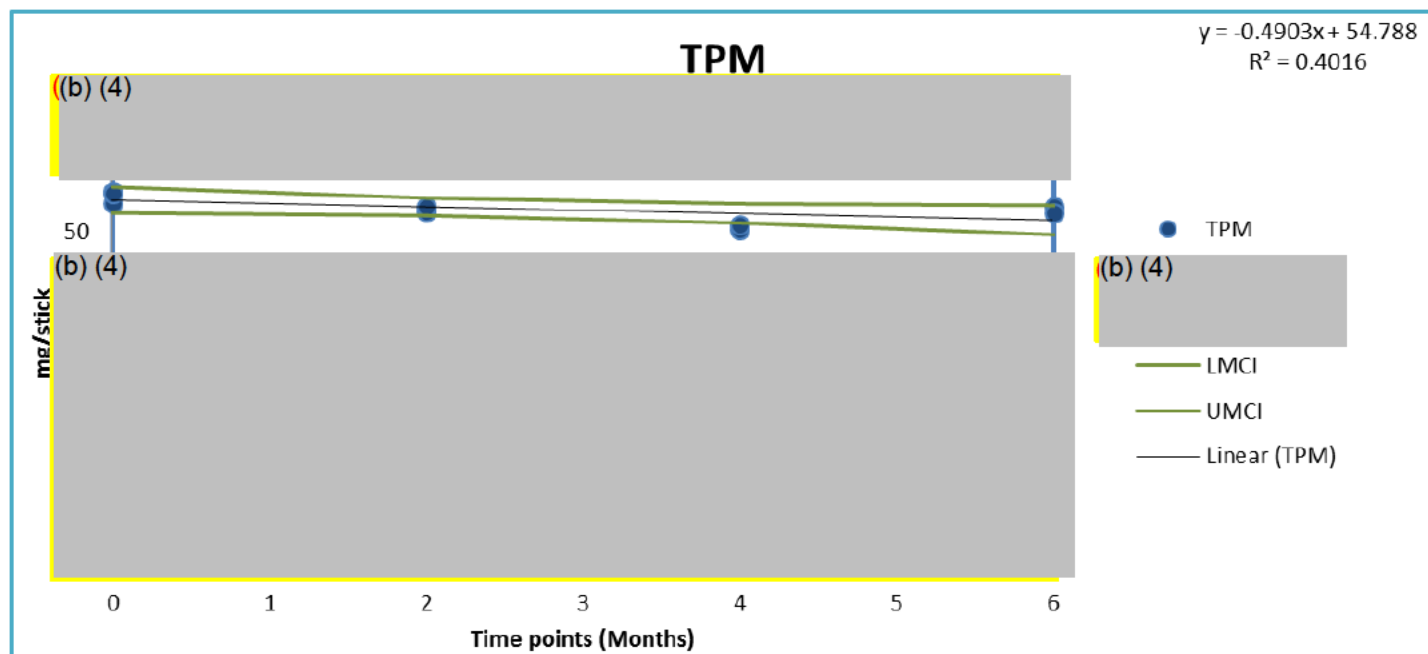
6.3.1.6 TPM

Figure 38 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 6 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 6 months.

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6.3.1.7 Phenol

$$y = 0.0379x + 1.246$$
$$R^2 = 0.2292$$

Figure 39 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 6 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 6 months.
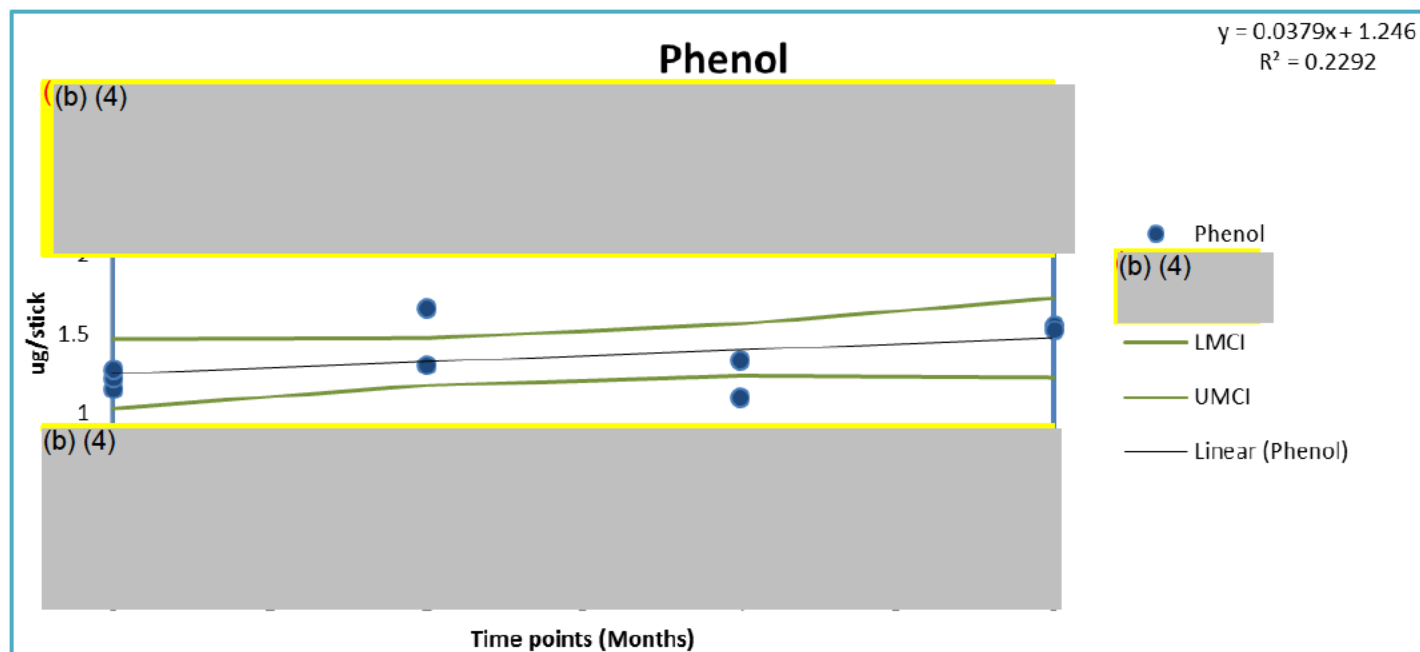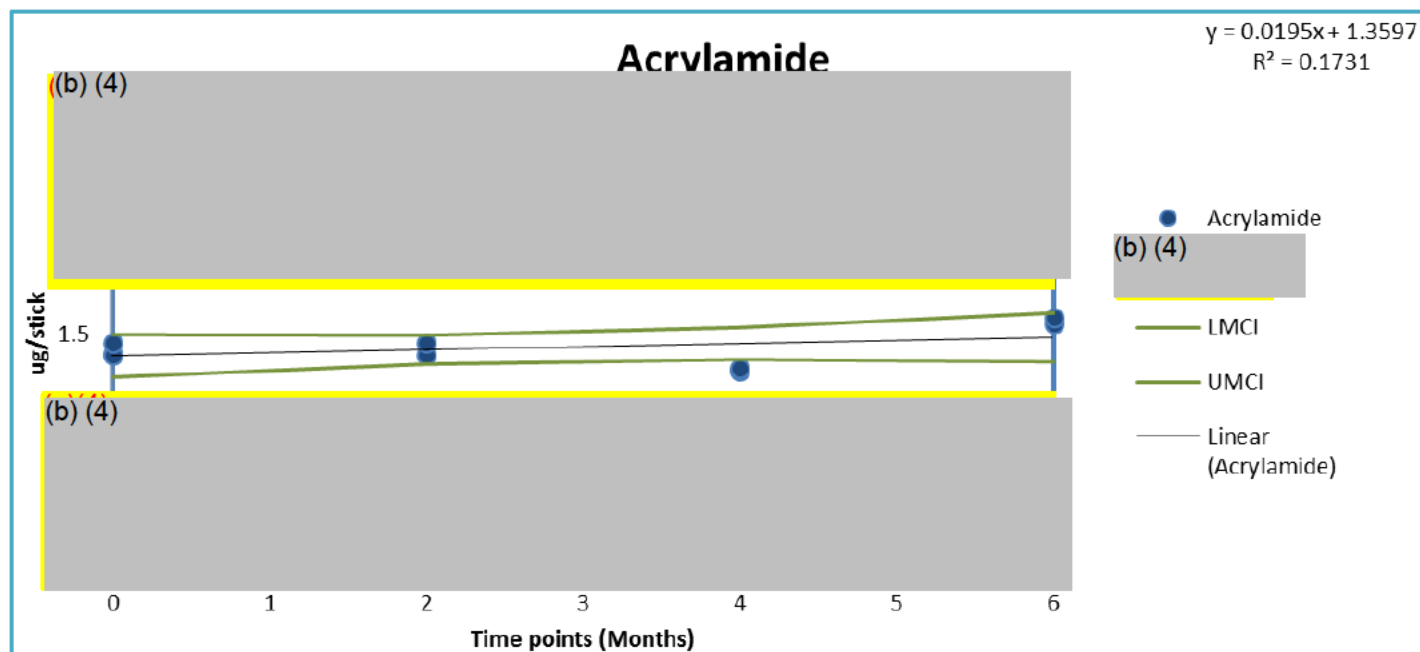
6.3.1.8 Acrylamide

Figure 40 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 6 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 6 months.

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6.3.1.9 Acetamide

Figure 41 Acetamide is not suitable for trend analysis since it was tested in less than 3 different time points. All the values obtained are inside the specifications and therefore Acetamide is considered stable for 6 months.

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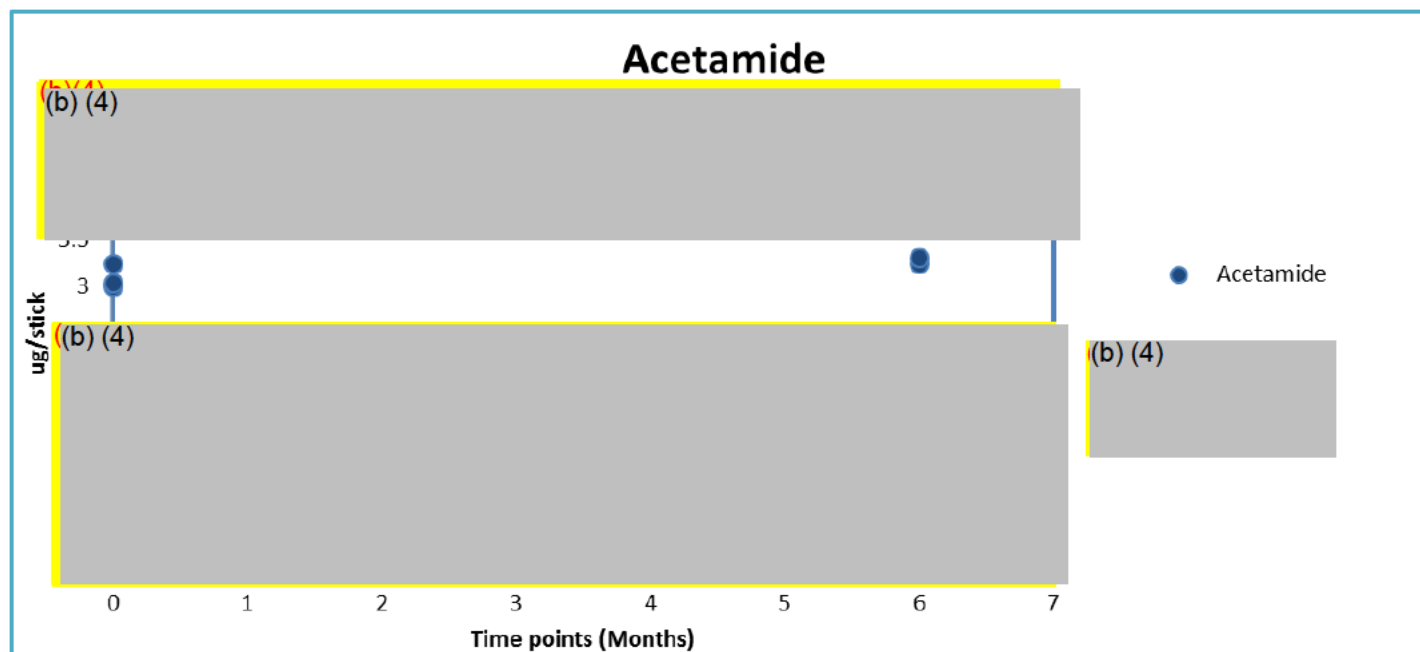
6.3.1.10 Acetaldehyde

Figure 42 Acetaldehyde is not suitable for trend analysis since it was tested in less than 3 different time points. All the values obtained are inside the specifications and therefore Acetaldehyde is considered stable for 6 months.
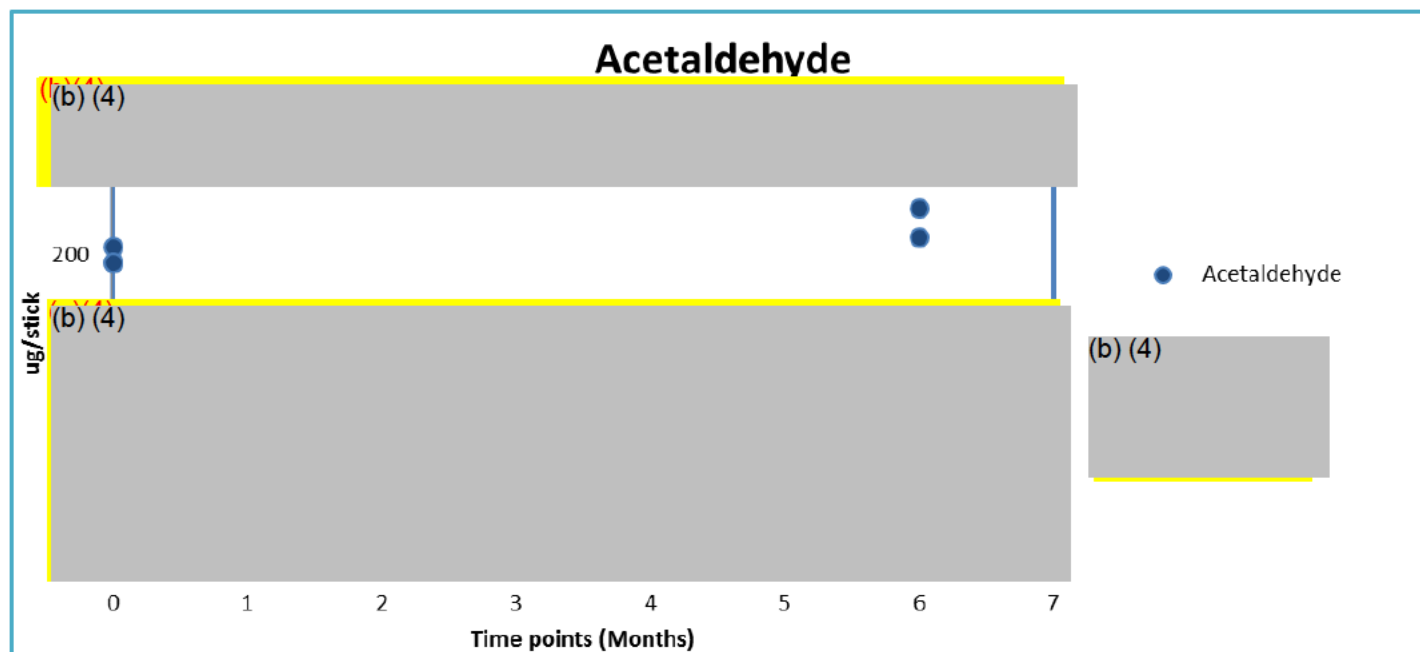
6.3.1.11 Butyraldehyde

Figure 43 Butyraldehyde is not suitable for trend analysis since it was tested in less than 3 different time points. All the values obtained are inside the specifications and therefore Butyraldehyde is considered stable for 6 months.

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6.3.1.12 Acrylonitrile

Figure 44 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 6 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 6 months.

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6.3.1.13 Isoprene

Figure 45 The reported values are well inside the specifications even with the overestimated values in T2 and T4 (see Chapter 5.2), therefore Isoprene is considered stable for 4 months.
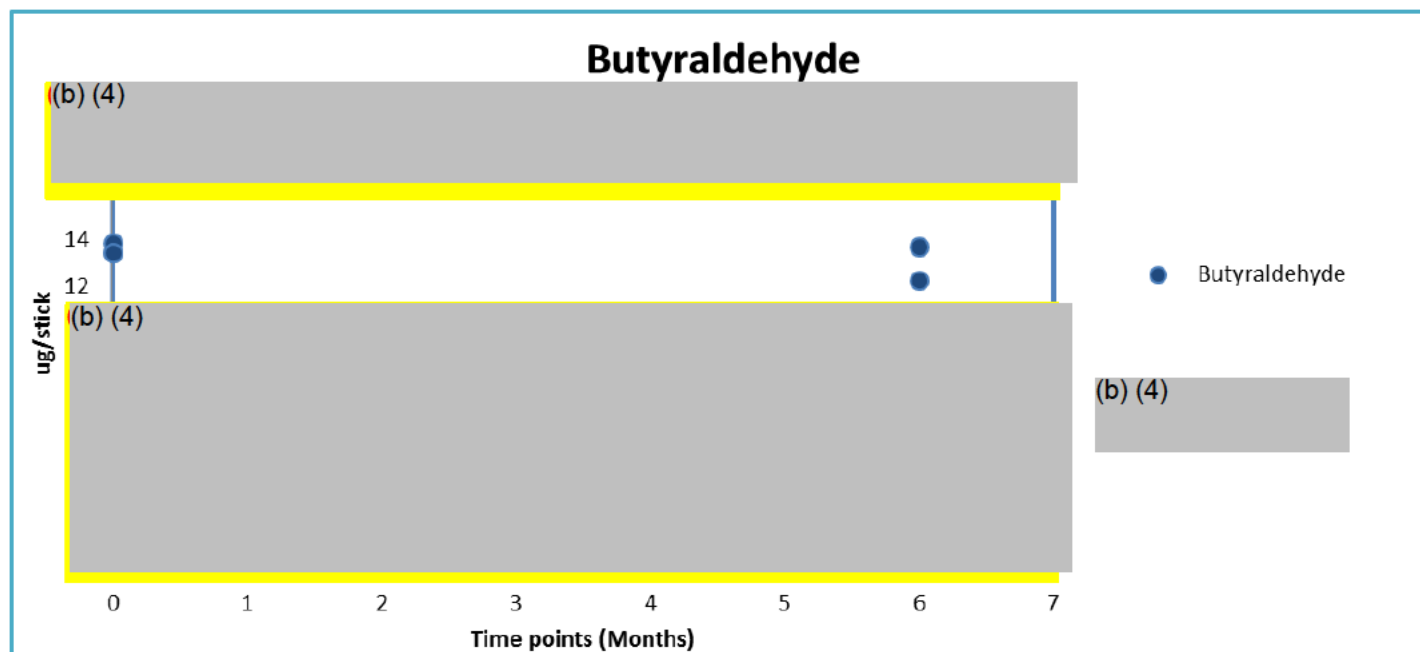
6.3.1.14 Pyridine

Figure 46 Pyridine is not suitable for trend analysis since it was tested in less than 3 different time points. All the values obtained are inside the specifications and therefore Pyridine is considered stable for 6 months.

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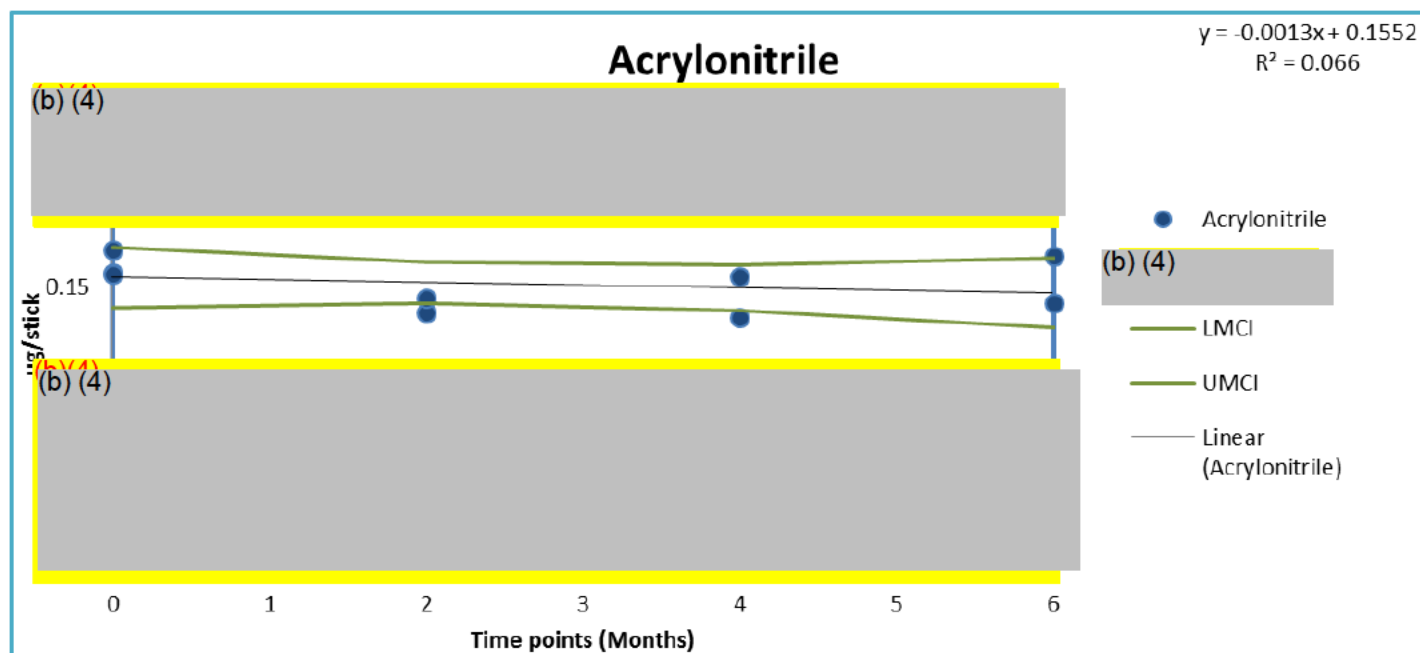Form Status: Effective
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6.3.1.15 Ammonia
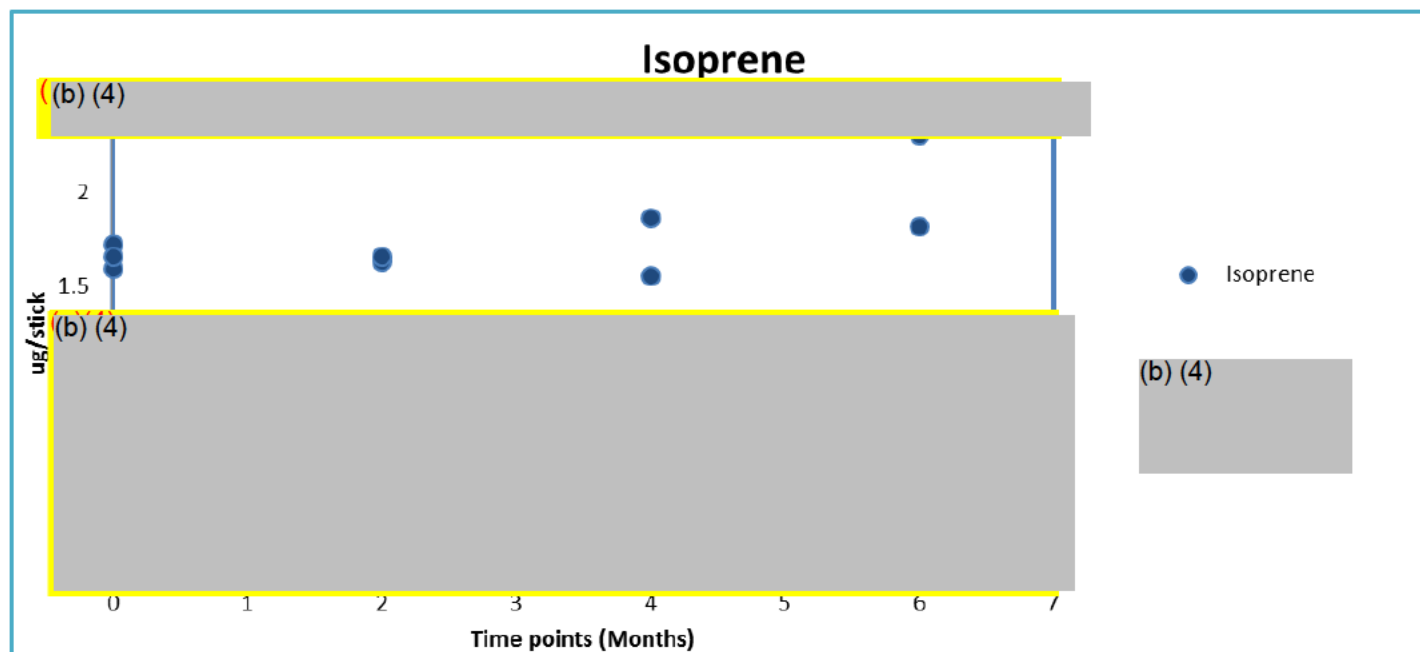

Figure 47 Ammonia is not suitable for trend analysis since it was tested in less than 3 different time points. All the values obtained are inside the specifications and therefore Ammonia is considered stable for 6 months.

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6.3.2 Physical Attributes Evaluation

(b) (4)

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6.3.3 Sensorial Evaluation

Sensorial evaluation results are described in details in a separate report [5].

(b) (4)

A shelf life of 6 months is considered as acceptable.

6.3.4 Visual inspection

(b) (4)

The visual quality of the tobacco sticks can be considered acceptable during 2 months storage in 30^{0}C 75%RH.

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7 Stability Assessment

Overall it can be concluded that the THS 2.2 Dorado I Vinny Low remained within specifications up to 12 months in the 22°C 60%RH and 30°C 35%RH conditions; and up to 4 months in the 30°C 75%RH.

In the conditions 22°C 60%RH all the product parameters were found stable for 12 months.

In the conditions 30°C 35%RH all the product parameters were found stable for 12 months.

In wet and very humid conditions 30°C 75%RH, all the product parameters were found stable for 6 months with the exception of:

-        Isoprene was found acceptable up to 4 months. Due to deviation described in Chapter 5.2 the stability until 6 months could not be demonstrated.

-        Visual aspect was found acceptable up to 2 months.

8 Related Documents

[1] P1 THS 2 2 EXPT004923_STABILITY STUDY PROTOCOL DORADO I MINT VINNY.doc

https://disco.app.pmi/disco/drl/objectId/0901d4ec805dd8b4

[2]   P1 Product specifications

https://disco.app.pmi/disco/drl/objectId/0901d4ec80572517

[3]   P1_PDev_SPE_DI Vinny Low menthol batch release specs.doc

https://disco.app.pmi/disco/drl/objectId/0901d4ec805e1a89

[4]   P1_PDev_SPE_DI Vinny low Performance Specifications.doc

https://disco.app.pmi/disco/drl/objectId/0901d4ec805e03a0

[5]   P1_CPD_SWP_Product monitoring__SS_004_2017_02_1_MRTP_DI Vinny Low_T12

http://rrpplm.app.pmi/Agile/PLMServlet?fromPCClient=true&module=ActivityHandler&requestUrl=module%3DActivityHandler%26opcode%3DdisplayObject%26classid%3D18387%26objid%3D229288%26tabid%3D%26

[6]   Scientific Report: PT_AL_Isoprene Investigation_PMI _RD_WKI_000383

https://disco.app.pmi/disco/drl/objectId/0901d4ec806191b5

9 Reference Documents

WHO Stability testing of active pharmaceutical ingredients and finished pharmaceutical products
ISO 3402:1999 Tobacco and tobacco products -- Atmosphere for conditioning and testing
ICH Q1(E) Evaluation of Stability Data

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10 Revision History for Stability Report

Version Nr	Description of change	Justification
1.0	Initial version.	NA
2.0	1. Alignment of vocabulary for specifications throughout the report. 2. In Chapter 6 Stability Data Evaluation description was clarified regarding conclusion about shelf life and truncation. 3. Correction in Figure titles in Chapter 6 of the earlier crossing time. For all tested parameters evaluated (b) (b) the earliest crossing time was written as 12 months for 22°C 60%RH and 30°C 35%RH and 6 months for 30°C 75% RH. This is now corrected to "over" 12 or 6 months in case the crossing time determined by "(b) was longer than the study length. 4. Chapter 7 Stability Assessment has been reviewed in order to conclude about product stability parameters and removed product shelf life recommendation.	1. Clarification that the specifications used are the product specifications. 2. This is a clarification about how data evaluation was done and reported. 3. The earliest crossing time was wrongly written for attributes where the (b) model determined earliest crossing time longer than the study duration. 4. The decision about product shelf life remains to the sponsor of the study.
3.0	1. Correction of CO, Triacetin, Phenol, Acrlyamide values for B-25902 30°C/35%RH for T4 time point in Table 10, Figure 20, 21, 23 and 24; based on CAPA-RRP-NEU-2017-237.	1. The CAPA has been initiated to align results reported in the study with OOT investigation done at T4 time point, by correcting results for CO, Triacetin, Phenol and Acrlyamide as described in the outcome of the investigation. The correction has no impact on the conclusions of the stability study. The investigations for OOS/OOT results are stored together with study documents.

11 Definitions and Abbreviations

Abbreviation	
CO	Carbon Monoxide
IP	Intermediate Precision
ISO	International Organization for Standardization
LMCI	95% lower mean confidence interval for the predicted values

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Abbreviation	
LSL	Lower Shelf Life specification limit
PDIMS	Product Development Information Management System
PMMTB	Philip Morris Manufacturing & Technology Bologna (Training Center)
QDP	Quantitative Descriptive Profile
RDLIMS	Research Development Laboratory Information Management System
R&D	Research and Development
RH	Relative Humidity
SDMS	Scientific Data Management System
THS	Tobacco Heating System
TO	Testing Order
TPM	Total Particulate Matter
USL	Upper Shelf Life specification limit
UMCI	95% upper mean confidence interval for the predicted values
WHO	World Health Organization

12 Appendices

12.1 Climatic Zones

Table 14 Climatic Zones

Climatic Zone	Definition	Long Term Testing Conditions
I	Temperated climate	21°C / 45% RH
II	Subtropical and Mediterranean Climate	25°C / 60% RH
III	Hot and dry climate	30°C / 35% RH
IVA	Hot and humid climate	30°C / 65% RH
IVB	Hot and very humid climate	30°C / 75% RH

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12.2 Equivalence List for Quality Documents

Table 15 CDocs and OMSP References

CDocs number	OMSP number
PMI_RD_FOR_000927	PMI-RRP-FOR-111545
PMI_RD_WKI_000383	PMI-RRP-WKI-111706
PMI_RD_WKI_000391	PMI-RRP-WKI-111709
PMI_RD_WKI_000477	PMI-RRP-WKI-111657
PMI_RD_WKI_000518	PMI-RRP-WKI-111729
PMI_RD_WKI_000530	PMI-RRP-WKI-111801
PMI_RD_WKI_000534	PMI-RRP-WKI-111743
PMI_RD_WKI_000584	PMI-RRP-WKI-111771
PMI_RD_WKI_000953	PMI-RRP-WKI-111604
PMI_RD_WKI_001392	PMI-RRP-WKI-111823
PMI_RD_SOP_000296	PMI-RRP-SOP-111558

12.3 Sample Traceability Matrix

Analyses have been requested through Testing orders in PDIMS (Table 16).

Results for aerosol chemistry and physical measurements are stored in SDMS under the corresponding project numbers. Results of sensory evaluation are stored in PDIMS.

Table 16 Sample Traceability Matrix

Time Point	Testing Order	RDLIMS Project Number
T0	TO-10587, TO-10588, TO-10589	RLS-ZRH-2016-18/19
T2	TO-10977, TO-10978, TO-10979	RLS-ZRH-2016-117/118
T4	TO-11414, TO-11416, TO-11419	RLS-ZRH-2016-192/195
T6	TO-11893, TO-11894, TO-11894	RLS-ZRH-2016-301
T9	TO-12683, TO-12684, TO-12742	RLS-ZRH-2016-445/446
T12	TO-13465, TO-13467, TO-13468	RLS-ZRH-2017-28/30