
APPENDIX A3.3-4 (V2)

STABILITY FINAL RESULTS (12 MONTHS) – REGULAR

TABLE OF CHANGES

Document	Summary of Changes
A3.3-4	Original submission STABILITY INTERMEDIATE RESULTS (6 MONTHS) – REGULAR
A3.3-4 (v2)	Amendment: replaces A3.3-4 STABILITY FINAL RESULTS (12 MONTHS) – REGULAR

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REPORT OF THE STABILITY STUDY FOR DORADO II RON THS 2.2 (EXPT004923)

Platform	P1								
Stability Study type	<table border="1"> <tr> <td>Initial Stability Study</td> <td><input type="checkbox"/></td> </tr> <tr> <td>In use</td> <td><input type="checkbox"/></td> </tr> <tr> <td>Post Change</td> <td><input checked="" type="checkbox"/></td> </tr> <tr> <td>Monitoring</td> <td><input type="checkbox"/></td> </tr> </table>	Initial Stability Study	<input type="checkbox"/>	In use	<input type="checkbox"/>	Post Change	<input checked="" type="checkbox"/>	Monitoring	<input type="checkbox"/>
Initial Stability Study	<input type="checkbox"/>								
In use	<input type="checkbox"/>								
Post Change	<input checked="" type="checkbox"/>								
Monitoring	<input type="checkbox"/>								

Name	Role	Justification	Date (dd-Mon yyyy)	Signature
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1 Purpose

The objective of this stability study is to demonstrate that the commercial product THS 2.2 Regular (Dorado II Ron) 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 ($30 \pm 2^\circ\text{C}$; $75 \pm 5\%$ RH and $30 \pm 2^\circ\text{C}$ $35 \pm 5\%$ RH) and ISO ($22 \pm 2^\circ\text{C}$; $60 \pm 5\%$ RH) storage conditions.

This report summarizes the results and trend analysis of the stability study STAB-2016_P1_R_1 performed according a protocol [1]. The study was performed in 3 production scale Dorado II Ron 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 II Ron

Product/ Test item	Consumable Batch Number	Finished Product Code	Manufacturing Date
THS 2.2 Dorado II Ron	B-25904 / 41-2397948	ME000004.02	18 Jan. 2016
	B-25905 / 41-2397950	ME000004.02	18 Jan. 2016
	B-25906 / 41-2382704	ME000004.02	14 Jan. 2016

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 $22 \pm 1^\circ\text{C}$, $60 \pm 3\%$ RH prior to aerosol generation.

Conditioning for physical analyses was performed as described in respective work instruction, inside open packs for at least 24 hours at $22 \pm 2^\circ\text{C}$ and $50 \pm 5\%$ RH.

Conditioning for sensorial evaluation was performed at $22 \pm 2^\circ\text{C}$ and $58 \pm 5\%$ RH at least 48 hours inside open packs.

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



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3.2 Aerosol Generation and Analyses

The atmosphere for aerosol generation was $22 \pm 2^\circ\text{C}$, $60 \pm 5\%$ 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 in (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	7.0	7.0 / 8.0	(b) (4)
	PMI_RD_WKI_000953	3.0	3.0 / 3.0	
Glycerin mg/stick	PMI_RD_WKI_000530	7.0	7.0 / 8.0	
	PMI_RD_WKI_000953	3.0	3.0 / 3.0	
CO mg/stick	PMI_RD_WKI_000530	7.0	7.0 / 8.0	
Triacetin mg/stick	PMI_RD_WKI_000530	7.0	7.0 / 8.0	
	PMI_RD_WKI_000953	3.0	3.0 / 3.0	
TPM mg/stick	PMI_RD_WKI_000530	7.0	7.0 / 8.0	
Phenol µg/stick	PMI_RD_WKI_000530	7.0	7.0 / 8.0	
	PMI_RD_WKI_000953	3.0	3.0 / 3.0	
Acrylamide µg/stick	PMI_RD_WKI_000530	7.0	7.0 / 8.0	
	PMI_RD_WKI_000953	3.0	3.0 / 3.0	
Acetamide µg/stick	PMI_RD_WKI_000530	7.0	7.0 / 8.0	
	PMI_RD_WKI_000584	7.0	7.0 / 7.0	
Acetaldehyde µg/stick	PMI_RD_WKI_000534	11.0	11.0 / 12.0	
	PMI_RD_WKI_000391	13.0	13.0 / 15.0	



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

(b) (4)

(b) (4)

3.3 Visual Inspection

(b) (4)

3.4 Sensorial Evaluation

(b) (4)



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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 II Ron (B-25904)	22°C±2°C / 60%RH±5%RH	January 29, 2016	MP S PF		MP S	MP S PF		MP S PF
	30°C±2°C / 75%RH±5%RH			MP S	MP S		C**	C**
	30°C±2°C / 35%RH±5%RH			MP S		MP S PF	MP S PF	MP S PF
Dorado II Ron (B-25905)	22°C±2°C / 60%RH±5%RH	January 29, 2016	MP S PF	MP S	MP S		MP S PF	MP S PF
	30°C±2°C / 75%RH±5%RH			MP S		MP S PF	C**	C**
	30°C±2°C / 35%RH±5%RH				MP S	MP S PF		MP S PF
Dorado II Ron (B-25906)	22°C±2°C / 60%RH±5%RH	January 29, 2016	MP S PF	MP S		MP S PF	MP S PF	MP S PF
	30°C±2°C / 75%RH±5%RH				MP S	MP S PF		C**
	30°C±2°C / 35%RH±5%RH			MP S	MP S		MP S PF	MP 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
- T2 – T9 - aerosol: 4 replicates/batch; (b) (4) 50 sticks/batch; Visual evaluation: 100 sticks/batch



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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 condition 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_R_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



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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 value, 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 value 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) software in case of trend analyses or conclusion about shelf life by comparing the reported value with the specification.

The shelf life obtained with (b) (4) is truncated to whole number. In case the shelf life calculated by (b) (4) is longer than the study duration than the shelf life will be equal to the study duration. (4)



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6.1 Storage Condition 22°C 60% RH

Table 5 B-25904 / 41-2397948 at 22°C 60% RH

B-25904 / 41-2397948	Unit	Specifications		Time Points (Months)						Degradation Rate	R^2	Severity Score
Test		Lower	Upper	0	2	4	6	9	12			
Nicotine	mg/stick	(b) (4)		1.25		1.12	1.13		1.15	-0.61%	0.35	0.2
Glycerin	mg/stick			4.9		4.5	4.6		4.5	-0.60%	0.68	0.4
CO	mg/stick			0.2		0.4	0.5		0.5	9.25%	0.80	7.4
Triacetin	mg/stick			0.6		0.5	0.6		0.5	-1.20%	0.42	0.5
Phenol	µg/stick			1.7		1.5	2.1		1.8	1.15%	0.16	0.2
Acrylamide	µg/stick			1.5		1.4	1.7		1.5	0.30%	0.02	0.0
Acetamide	µg/stick			3.1			3.1		3.0	-0.11%	0.15	0.0
Acetaldehyde	µg/stick			197			200		183	-0.57%	0.59	0.3
Butyraldehyde	µg/stick			13.7			12.8		11.8	-1.14%	1.00	1.1
Acrylonitrile	µg/stick			0.16		0.14	0.15		0.13	-1.14%	0.85	1.0
Isoprene	µg/stick			1.65					1.47	NA	NA	NA
Pyridine	µg/stick			7.4			8.1		7.7	0.37%	0.23	0.1
Ammonia	µg/stick			13.0			10.6		9.8	-2.09%	0.93	1.9
TPM	mg/stick			56		53	53		51	-0.75%	0.91	0.7
(b) (4)												



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Table 6 B-25905 / 41-2397950 at 22°C 60% RH

B-25905 / 41-2397950	Unit	Specifications		Time Points (Months)						Degradation Rate	R^2	Severity Score
		Lower	Upper	0	2	4	6	9	12			
Test												
Nicotine	mg/stick	(b) (4)		1.18	1.15	1.11		1.14	1.12	-0.29%	0.37	0.1
Glycerin	mg/stick			4.8	5.1	4.6		4.4	4.6	-0.76%	0.51	0.4
CO	mg/stick			0.2	0.5	0.3		0.5	0.5	6.57%	0.46	3.0
Triacetin	mg/stick			0.6	0.5	0.5		0.5	0.4	-1.73%	0.89	1.5
Phenol	µg/stick			1.5	1.5	1.5		1.4	1.7	0.54%	0.10	0.1
Acrylamide	µg/stick			1.4	1.5	1.4		1.4	1.5	0.18%	0.07	0.0
Acetamide	µg/stick			3.0				3.1	3.0	-0.09%	0.17	0.0
Acetaldehyde	µg/stick			185				175	197	0.27%	0.08	0.0
Butyraldehyde	µg/stick			13.0				11.8	12.8	-0.36%	0.19	0.1
Acrylonitrile	µg/stick			0.15	0.15	0.12		0.13	0.13	-1.03%	0.41	0.4
Isoprene	µg/stick			1.55				1.51	1.37	-0.80%	0.70	0.6
Pyridine	µg/stick			7.3				7.9	7.8	0.67%	0.85	0.6
Ammonia	µg/stick			13.0				10.2	9.5	-2.31%	1.00	2.3
TPM	mg/stick			55	54	53		50	51	-0.67%	0.84	0.6

(b) (4)



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Table 7 B-25906 / 41-2382704 at 22°C 60% RH

B-25906 / 41-2382704	Unit	Specifications		Time Points (Months)						Degradation Rate	R^2	Severity Score
		Lower	Upper	0	2	4	6	9	12			
Nicotine	mg/stick	(b) (4)		1.24	1.15		1.16	1.23	1.13	-0.33%	0.16	0.1
Glycerin	mg/stick			4.7	5.0		4.9	5.0	4.3	-0.54%	0.22	0.1
CO	mg/stick			0.2	0.5		0.5	0.5	0.5	4.53%	0.40	1.8
Triacetin	mg/stick			0.5	0.6		0.6	0.5	0.4	-1.65%	0.43	0.7
Phenol	µg/stick			1.5	1.8		2.1	1.9	1.7	1.09%	0.14	0.1
Acrylamide	µg/stick			1.4	1.4		1.8	1.5	1.4	0.38%	0.02	0.0
Acetamide	µg/stick			3.1			3.3	2.9	3.0	-0.22%	0.06	0.0
Acetaldehyde	µg/stick			187			200	181	195	0.14%	0.02	0.0
Butyraldehyde	µg/stick			13.0			12.7	12.2	12.8	-0.25%	0.28	0.1
Acrylonitrile	µg/stick			0.15	0.15		0.15	0.13	0.13	-1.37%	0.61	0.8
Isoprene	µg/stick			1.62				1.59	1.40	-0.92%	0.59	0.5
Pyridine	µg/stick			7.1			8.3	8.0	7.4	0.39%	0.07	0.0
Ammonia	µg/stick			12.3			10.2	10.0	9.3	-2.04%	0.94	1.9
TPM	mg/stick			56	55		54	53	50	-0.77%	0.87	0.7

(b) (4)



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6.1.1 Mainstream Aerosol Evaluation

6.1.1.1 Nicotine

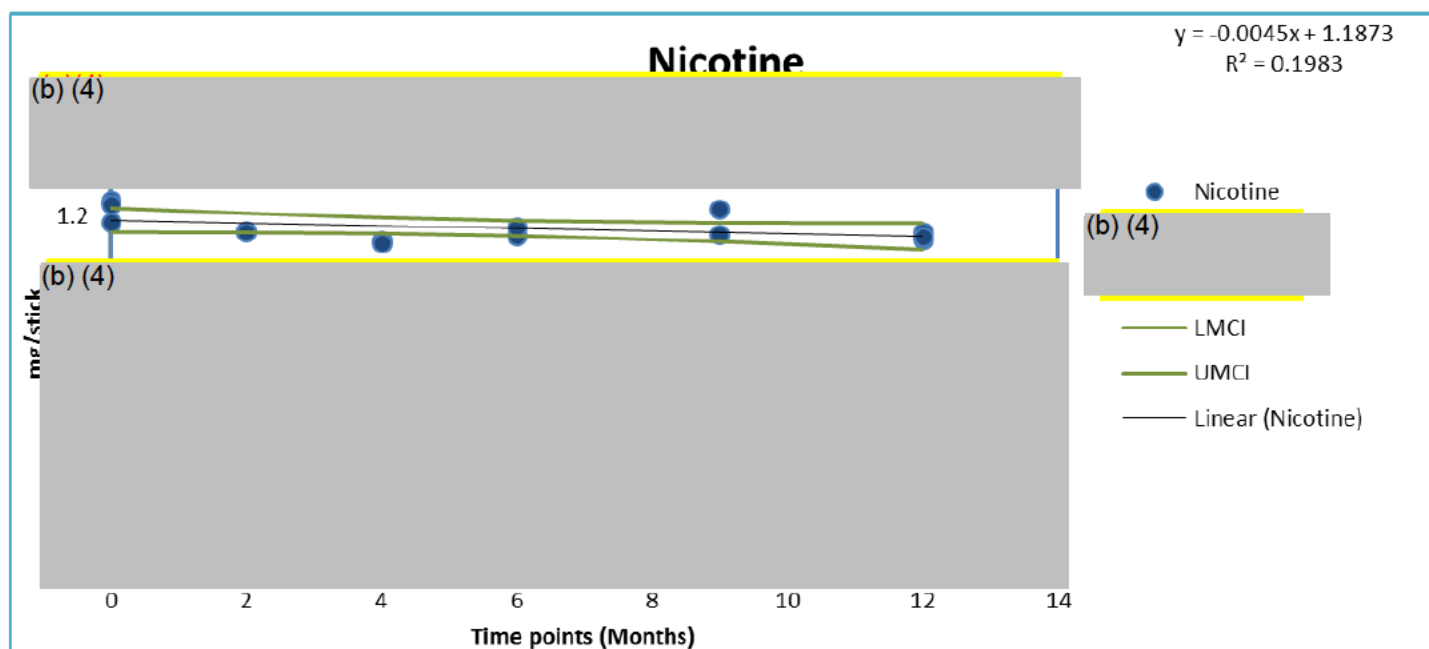


Figure 1 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.



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6.1.1.2 Glycerin

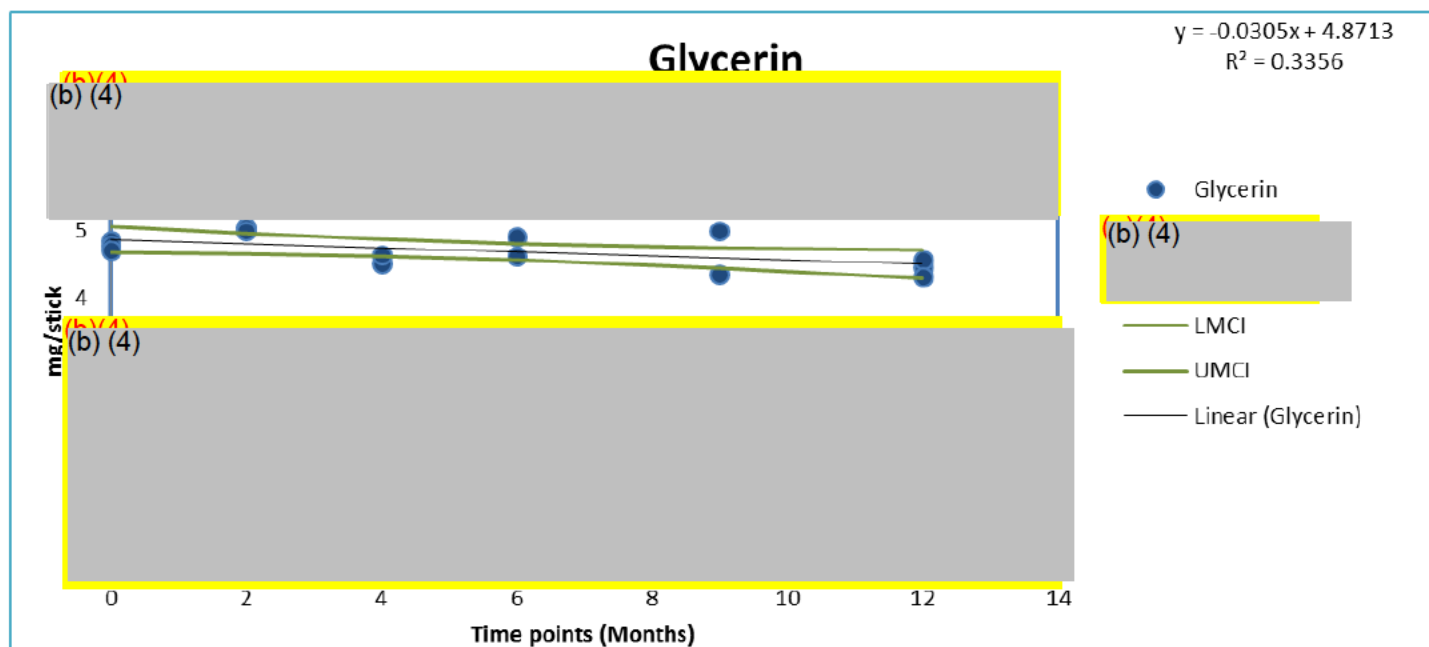


Figure 2 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.



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6.1.1.3 CO

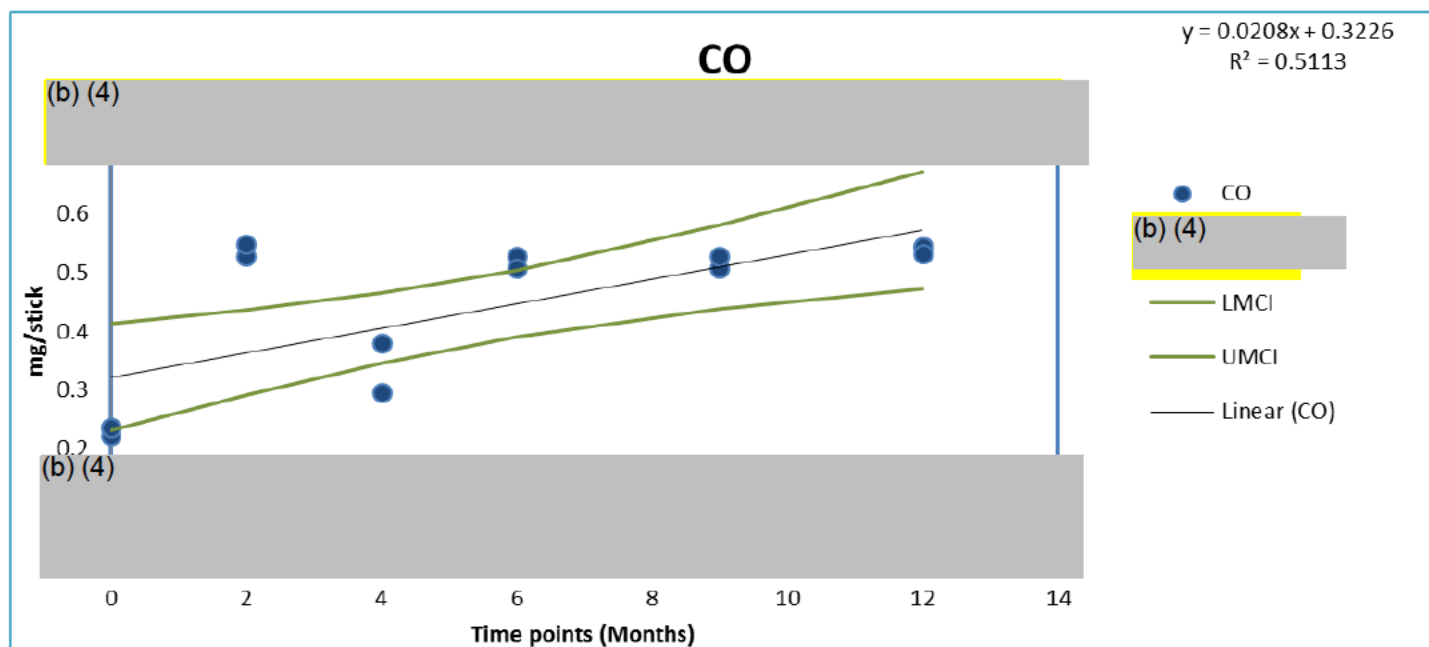


Figure 3 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.



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6.1.1.4 Triacetin

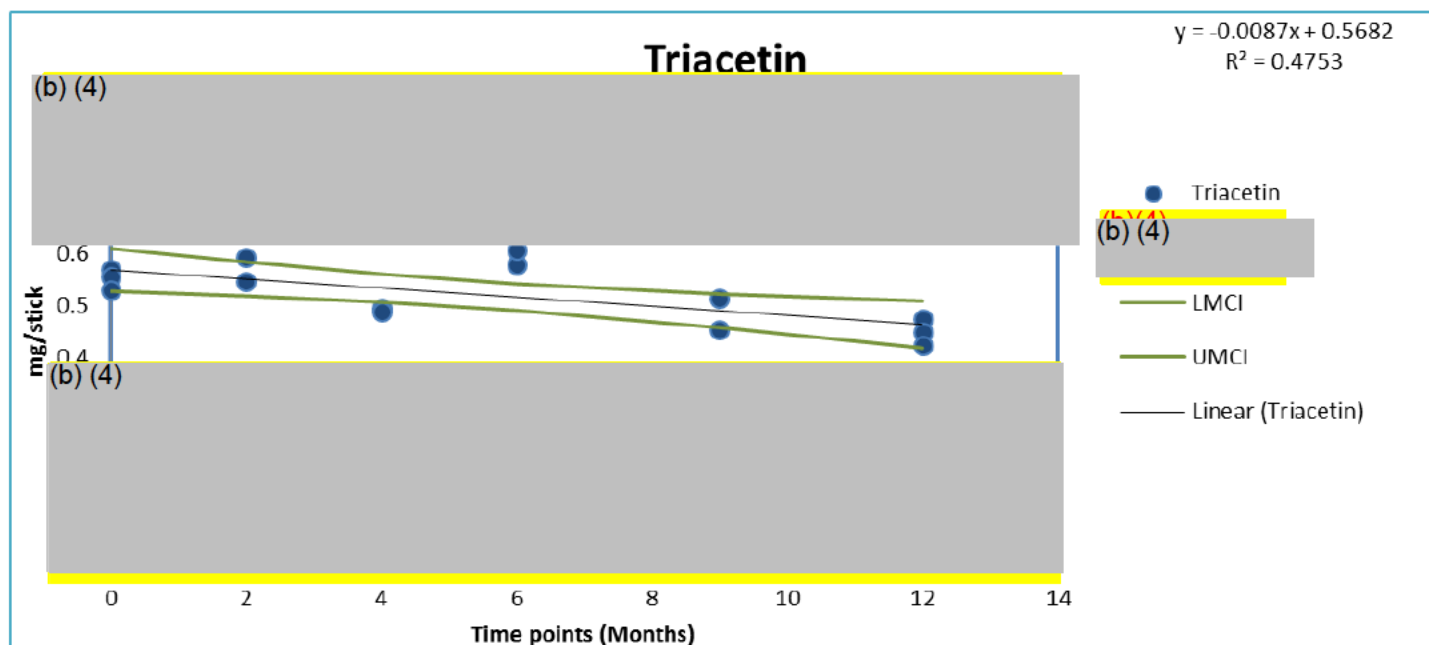


Figure 4 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.



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6.1.1.5 TPM

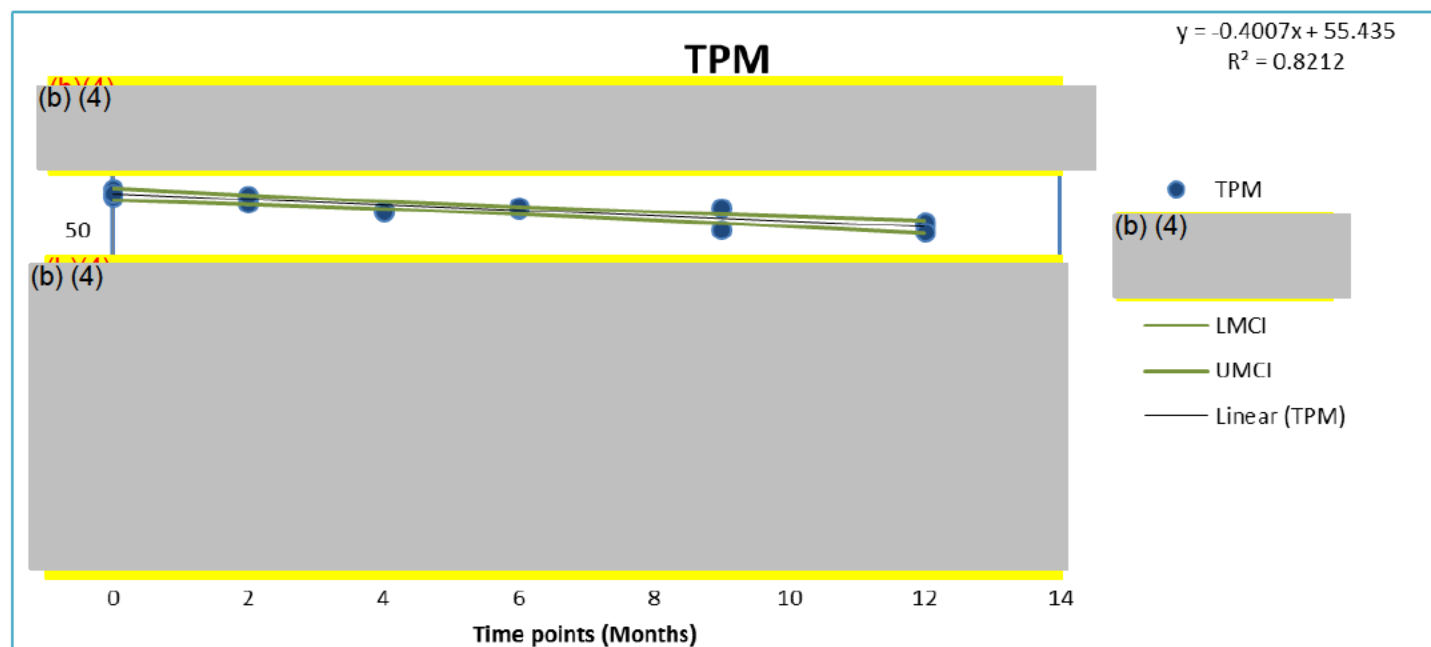


Figure 5 The best model accepted at the significance level of 0.25 has Different intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.



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6.1.1.6 Phenol

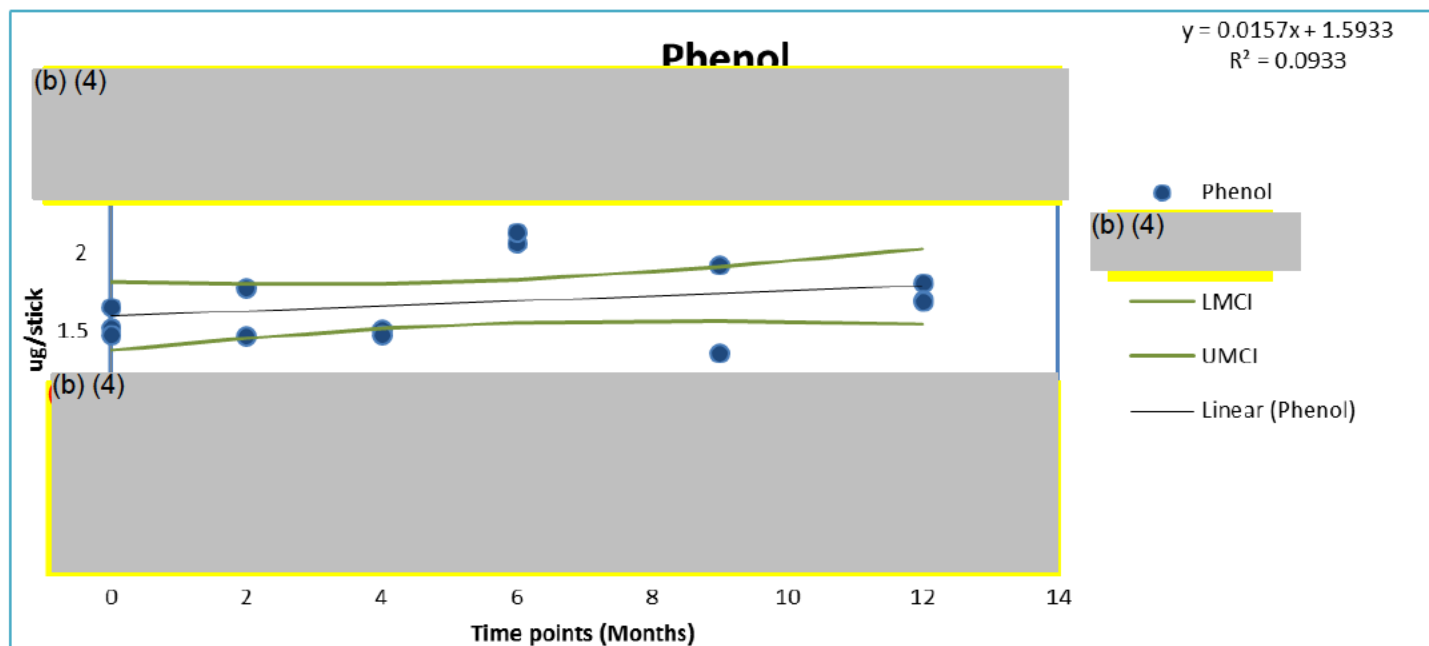


Figure 6 The best model accepted at the significance level of 0.25 has Different intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.



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Form Status: Effective
Form Effective Date: See EDMS

6.1.1.7 Acrylamide

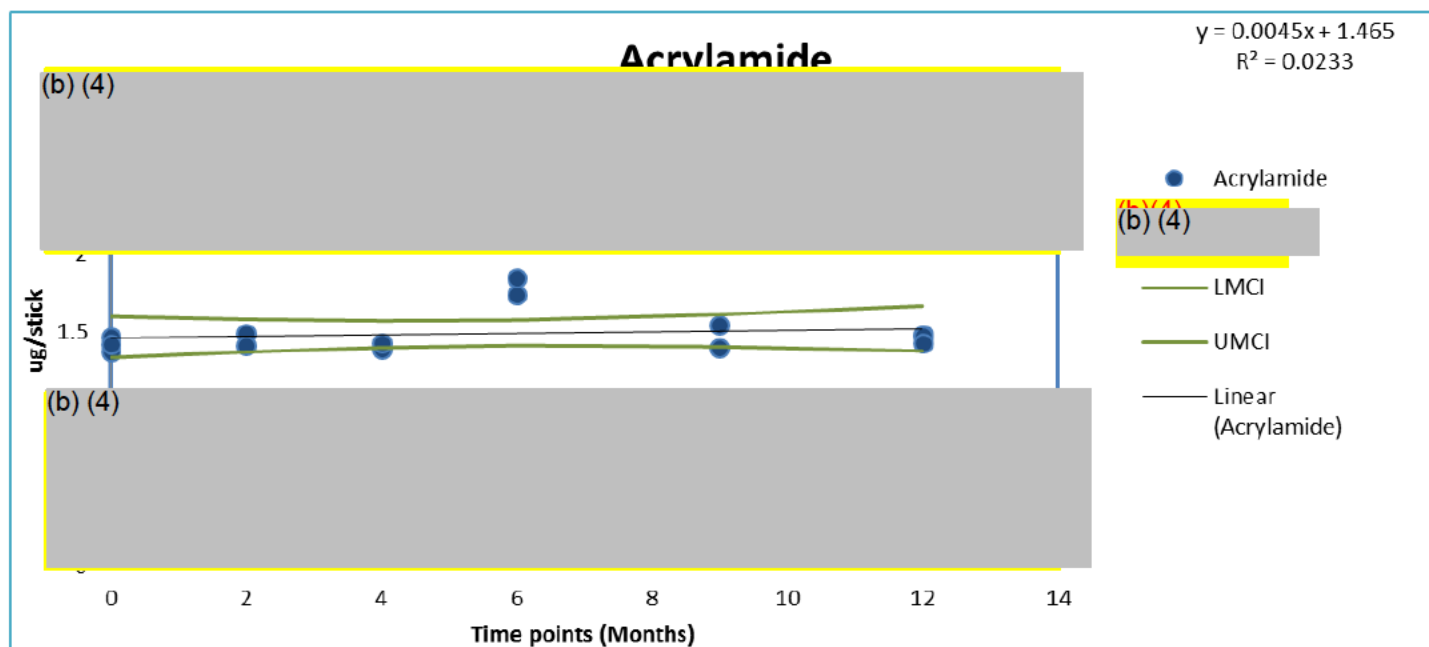


Figure 7 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.



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Form Status: Effective
Form Effective Date: See EDMS

6.1.1.8 Acetamide

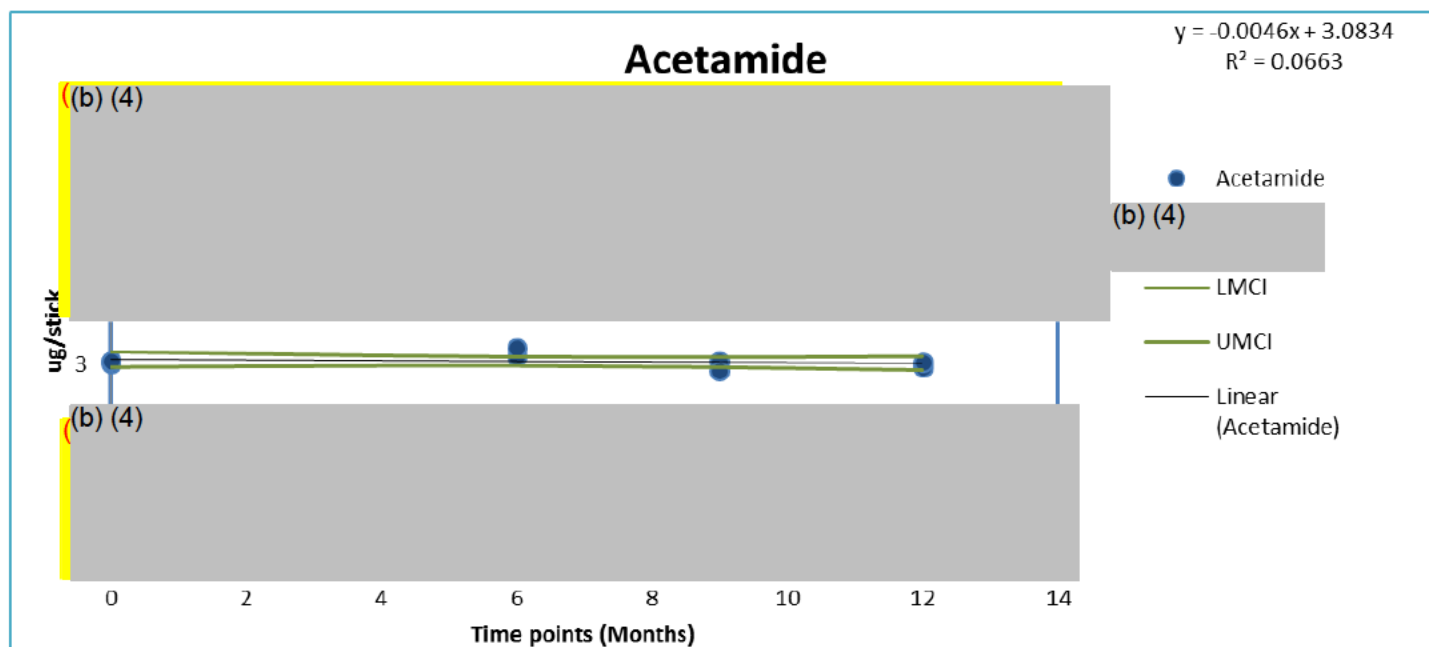


Figure 8 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.



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Form Status: Effective
Form Effective Date: See EDMS

6.1.1.9 Acetaldehyde

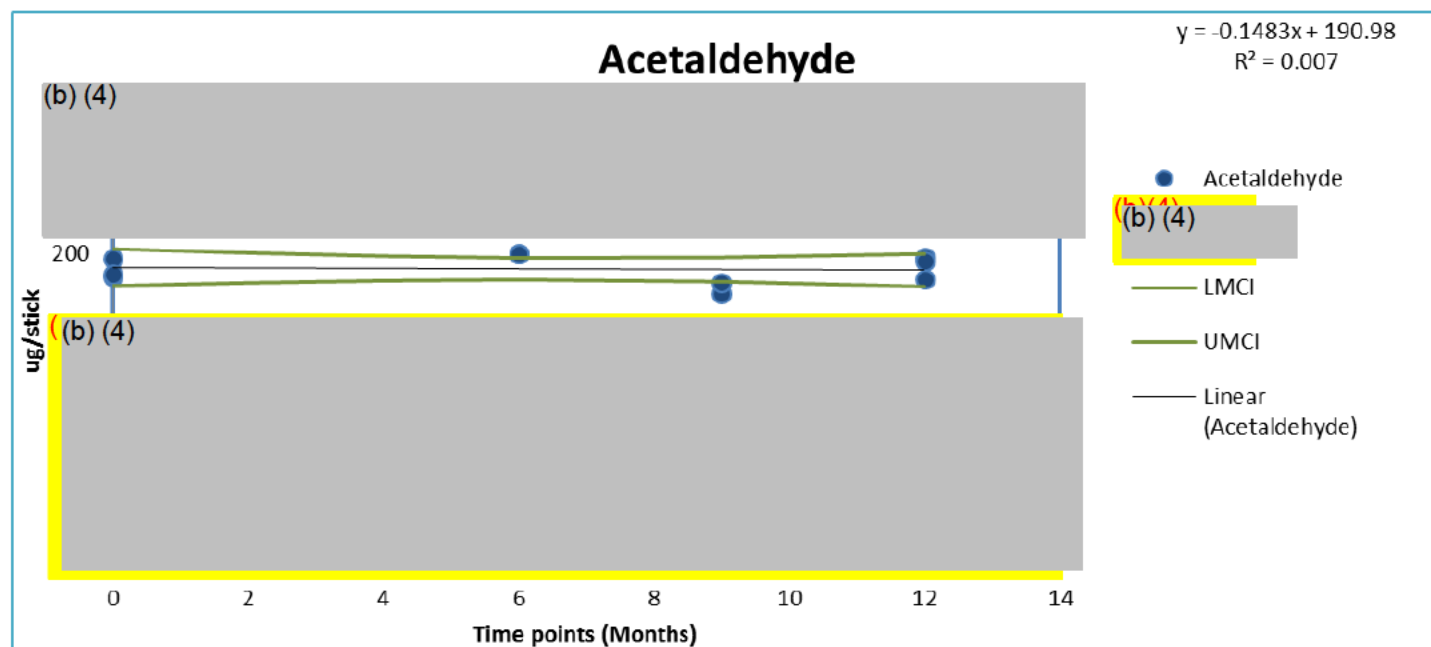


Figure 9 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.



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Form Status: Effective
Form Effective Date: See EDMS

6.1.1.10 Butyraldehyde

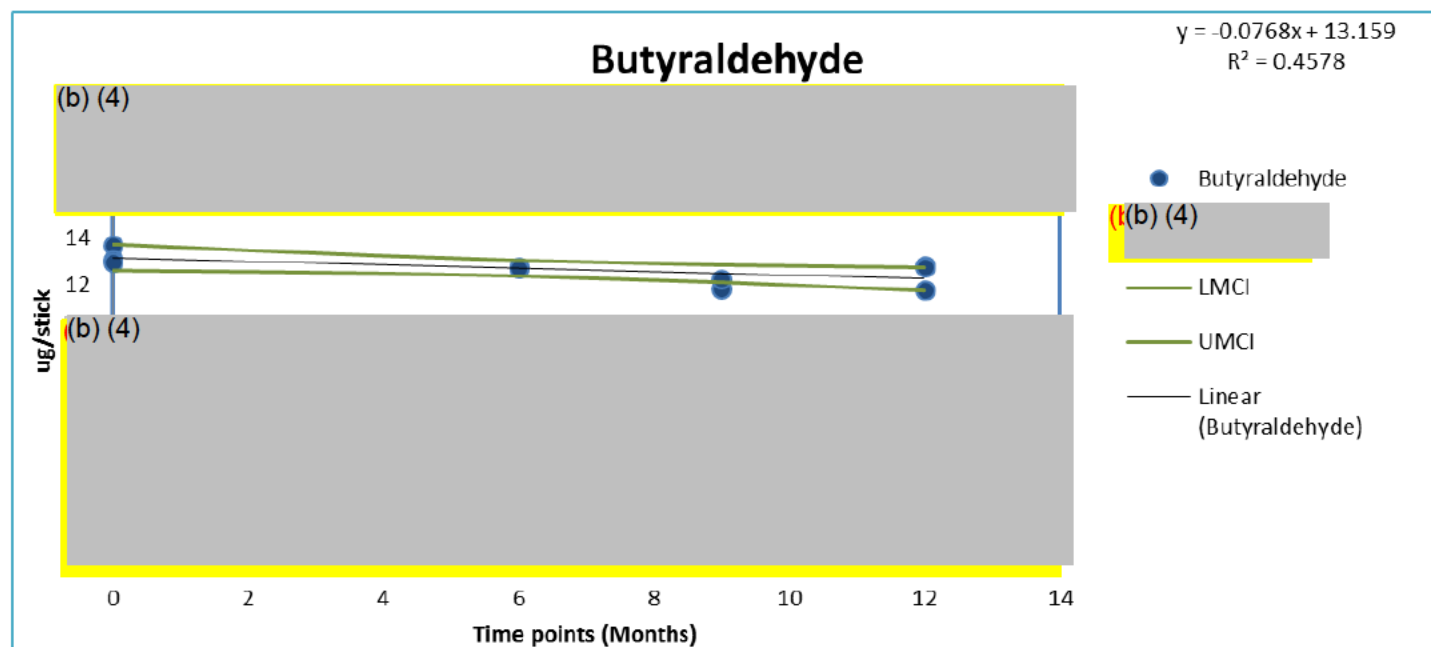


Figure 10 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.



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6.1.1.11 Acrylonitrile

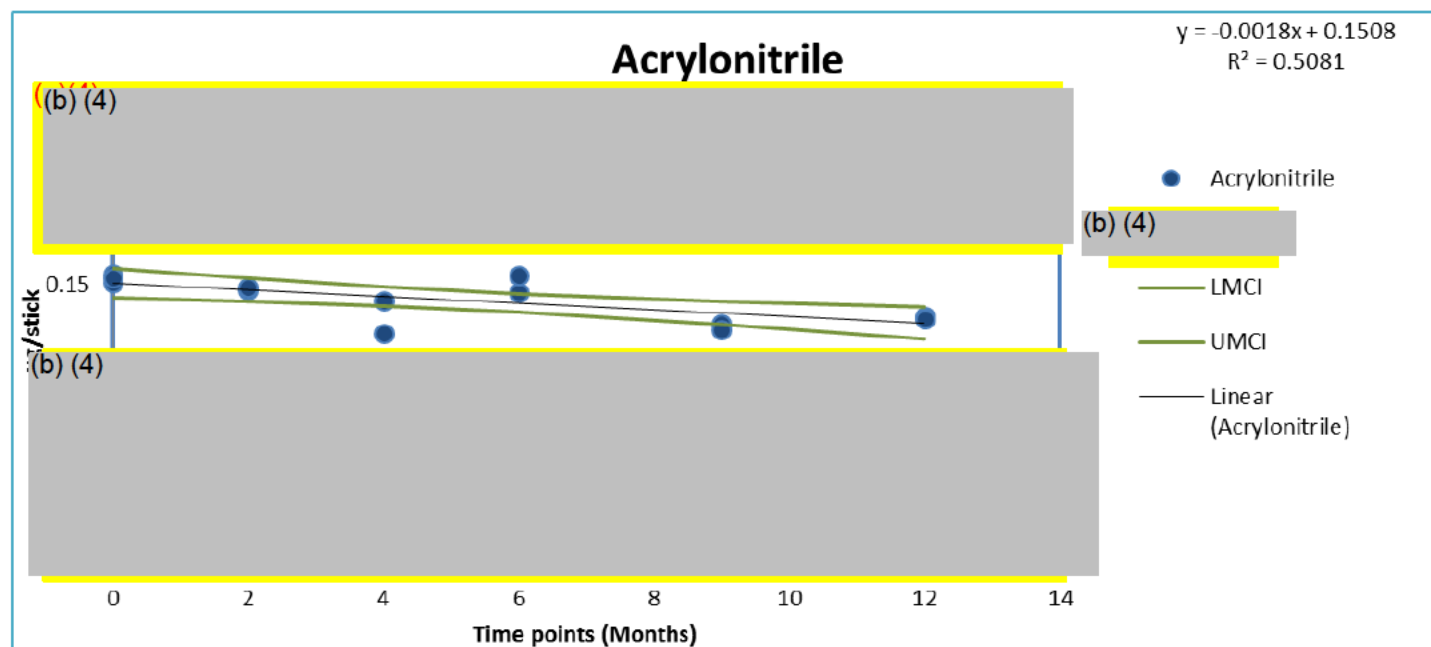


Figure 11 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.



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6.1.1.12 Isoprene

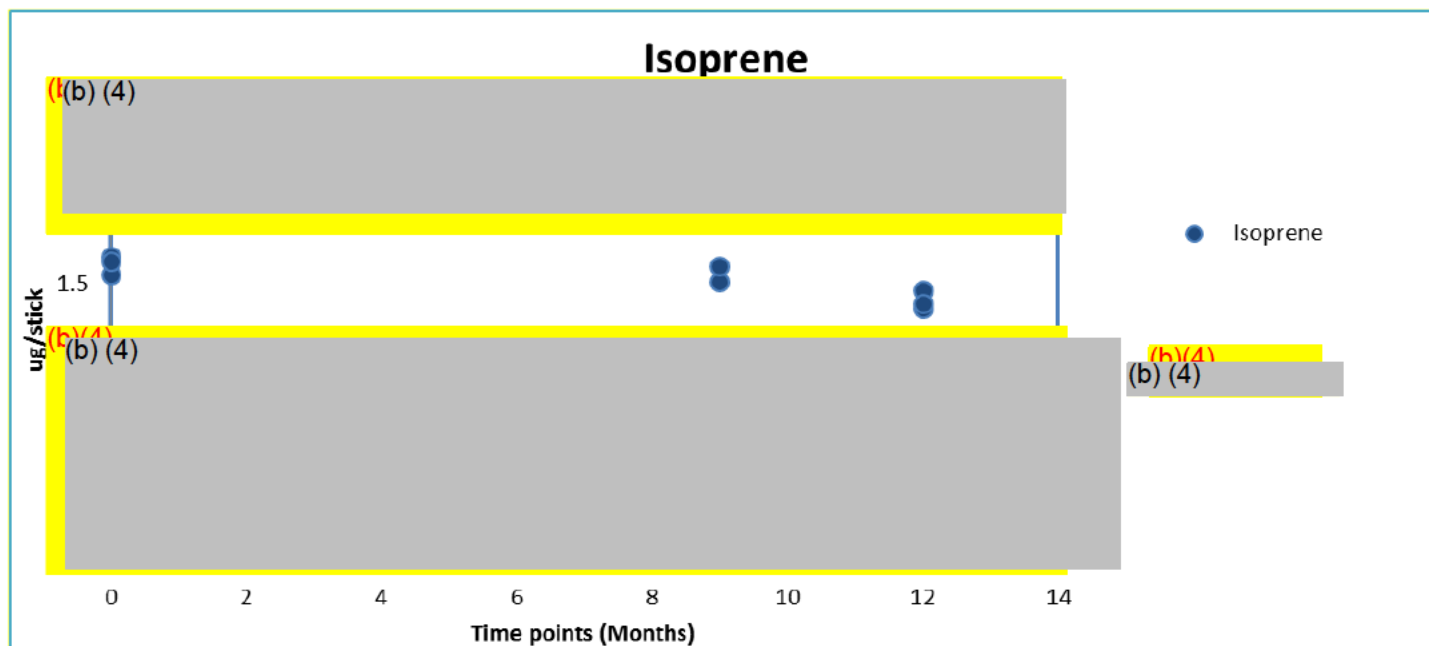


Figure 12 There is no obvious change over time in Isoprene level and all the values are well inside the specifications, therefore Isoprene is considered stable for 12 months.



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6.1.1.13 Pyridine

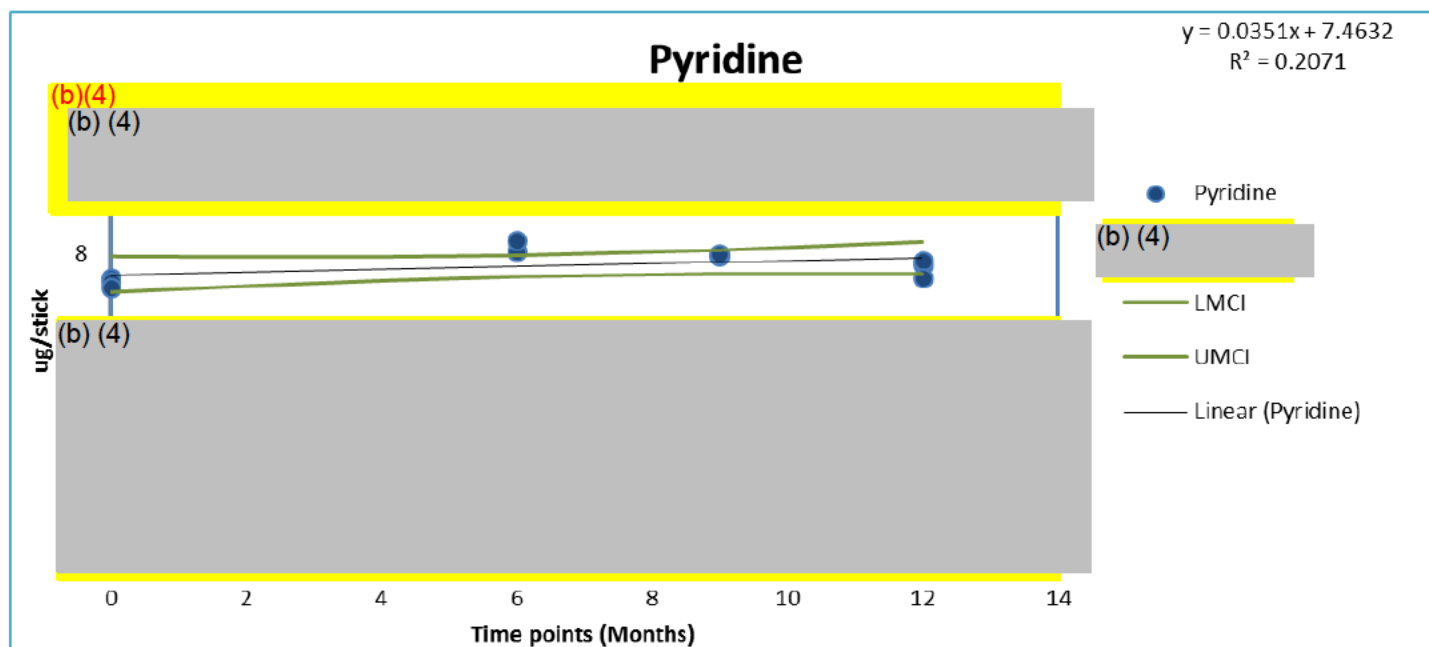


Figure 13 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.



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Form Status: Effective
Form Effective Date: See EDMS

6.1.1.14 Ammonia

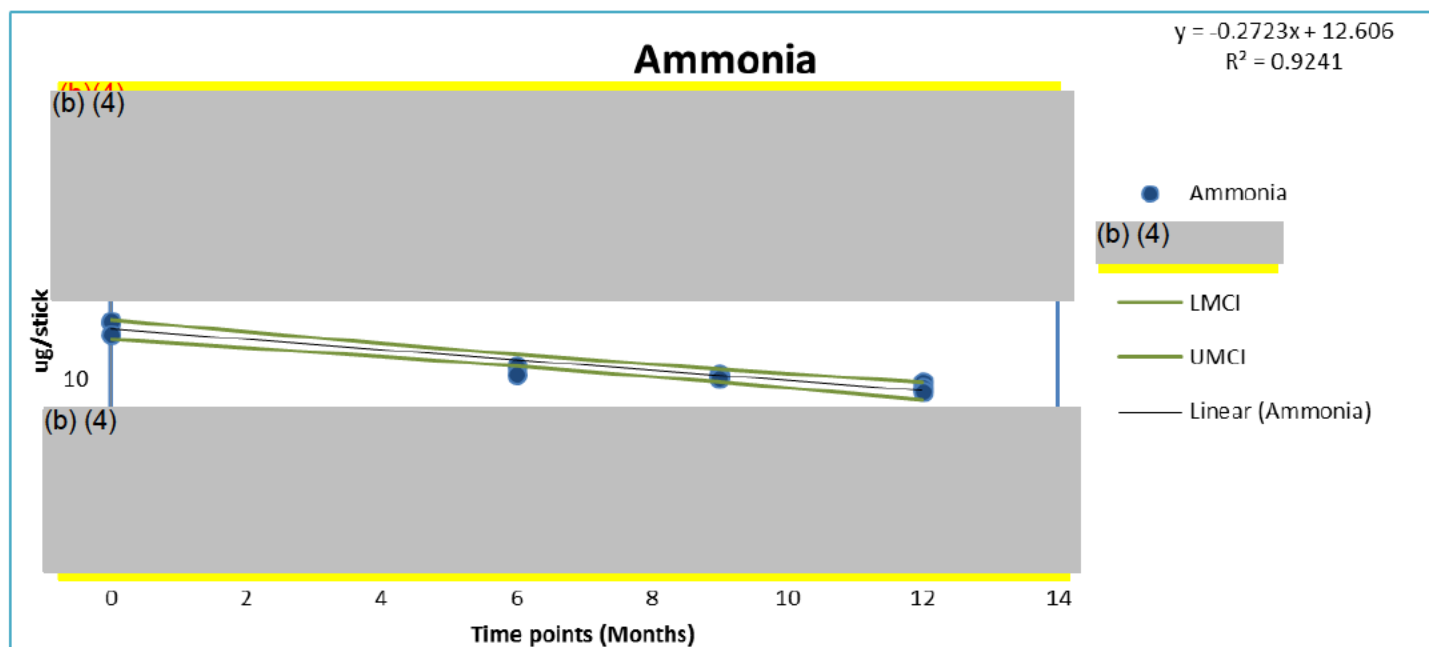


Figure 14 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.



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Form Status: Effective

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6.1.2 Physical Attributes Evaluation

(b) (4)



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Form Status: Effective

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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). 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 be considered as acceptable.

6.1.4 Visual inspection

(b) (4)

The visual quality of the tobacco sticks was found acceptable from visual point of view after 9 months of storage, however they were considered not acceptable after 12 months of storage in 22°C 60% RH.



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Form Status: Effective

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Form Effective Date: See EDMS

6.2 Storage Condition 30°C 35% RH

Table 8 B-25904 / 41-2397948 at 30°C 35% RH

B-25904 / 41-2397948	Unit	Specifications		Time Points (Months)						Degradation Rate	R^2	Severity Score
		Lower	Upper	0	2	4	6	9	12			
Test												
Nicotine	mg/stick	(b) (4)		1.25	1.09		1.18	1.17	1.09	-0.60%	0.25	0.2
Glycerin	mg/stick			4.9	4.7		5.0	4.2	4.3	-1.01%	0.57	0.6
CO	mg/stick			0.2	0.5		0.5	0.5	0.5	5.11%	0.49	2.5
Triacetin	mg/stick			0.6	0.5		0.6	0.4	0.4	-1.84%	0.39	0.7
Phenol	µg/stick			1.7	1.4		2.4	1.6	1.6	0.39%	0.01	0.0
Acrylamide	µg/stick			1.5	1.3		1.9	1.3	1.3	-0.58%	0.03	0.0
Acetamide	µg/stick			3.1			3.4	3.2	2.8	-0.54%	0.13	0.1
Acetaldehyde	µg/stick			197			188	189	190	-0.32%	0.62	0.2
Butyraldehyde	µg/stick			13.7			11.9	12.0	11.4	-1.37%	0.89	1.2
Acrylonitrile	µg/stick			0.16	0.14		0.16	0.12	0.14	-0.96%	0.28	0.3
Isoprene	µg/stick			1.65				1.50	1.44	-1.03%	1.00	1.0
Pyridine	µg/stick			7.4			8.9	8.0	8.1	0.65%	0.17	0.1
Ammonia	µg/stick			13.0			8.5	7.3	6.9	-4.22%	0.93	3.9
TPM	mg/stick			56	53		54	50	48	-1.06%	0.80	0.8

(b) (4)



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Table 9 B-25905 / 41-2397950 at 30°C 35% RH

B-25905 / 41-2397950	Unit	Specifications		Time Points (Months)						Degradation Rate	R^2	Severity Score
		Lower	Upper	0	2	4	6	9	12			
Test												
Nicotine	mg/stick	(b) (4)		1.18		1.13	1.10		1.09	-0.61%	0.77	0.5
Glycerin	mg/stick			4.8		4.5	4.6		4.3	-0.89%	0.94	0.8
CO	mg/stick			0.2		0.3	0.6		0.5	10.59%	0.70	7.4
Triacetin	mg/stick			0.6		0.5	0.5		0.4	-1.63%	0.87	1.4
Phenol	µg/stick			1.5		1.7	1.9		1.4	-0.59%	0.05	0.0
Acrylamide	µg/stick			1.4		1.4	1.6		1.3	-0.41%	0.04	0.0
Acetamide	µg/stick			3.0			3.4		2.8	-0.58%	0.14	0.1
Acetaldehyde	µg/stick			185			200		189	0.17%	0.07	0.0
Butyraldehyde	µg/stick			13.0			12.2		11.6	-0.94%	0.99	0.9
Acrylonitrile	µg/stick			0.15		0.13	0.14		0.12	-1.33%	0.60	0.8
Isoprene	µg/stick			1.55					1.26	NA	NA	NA
Pyridine	µg/stick			7.3			8.0		7.6	0.32%	0.18	0.1
Ammonia	µg/stick			13.0			8.1		6.8	-4.20%	0.90	3.8
TPM	mg/stick			55		51	53		48	-0.99%	0.83	0.8

(b) (4)



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Table 10 B-25906 / 41-2382704 at 30°C 35% RH

B-25906 / 41-2382704	Unit	Specifications		Time Points (Months)						Degradation Rate	R ²	Severity Score
Test		Lower	Upper	0	2	4	6	9	12			
Nicotine	mg/stick	(b) (4)		1.24	1.14	1.09		1.18	1.10	-0.53%	0.25	0.1
Glycerin	mg/stick			4.7	5.0	4.5		4.7	4.2	-0.84%	0.52	0.4
CO	mg/stick			0.2	0.5	0.3		0.5	0.5	5.46%	0.45	2.5
Triacetin	mg/stick			0.5	0.6	0.5		0.5	0.4	-1.88%	0.81	1.5
Phenol	µg/stick			1.5	1.8	1.6		1.9	1.6	0.68%	0.09	0.1
Acrylamide	µg/stick			1.4	1.4	1.3		1.4	1.3	-0.57%	0.39	0.2
Acetamide	µg/stick			3.1				3.0	2.7	-0.74%	0.65	0.5
Acetaldehyde	µg/stick			187				192	199	0.49%	0.84	0.4
Butyraldehyde	µg/stick			13.0				12.3	12.0	-0.59%	1.00	0.6
Acrylonitrile	µg/stick			0.15	0.14	0.13		0.13	0.13	-0.97%	0.46	0.4
Isoprene	µg/stick			1.62				1.65	1.45	-0.62%	0.34	0.2
Pyridine	µg/stick			7.1				7.9	7.8	0.84%	0.82	0.7
Ammonia	µg/stick			12.3				7.2	6.9	-3.95%	0.96	3.8
TPM	mg/stick			56	55	51		50	48	-1.13%	0.91	1.0



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6.2.1 Mainstream Aerosol Evaluation

6.2.1.1 Nicotine

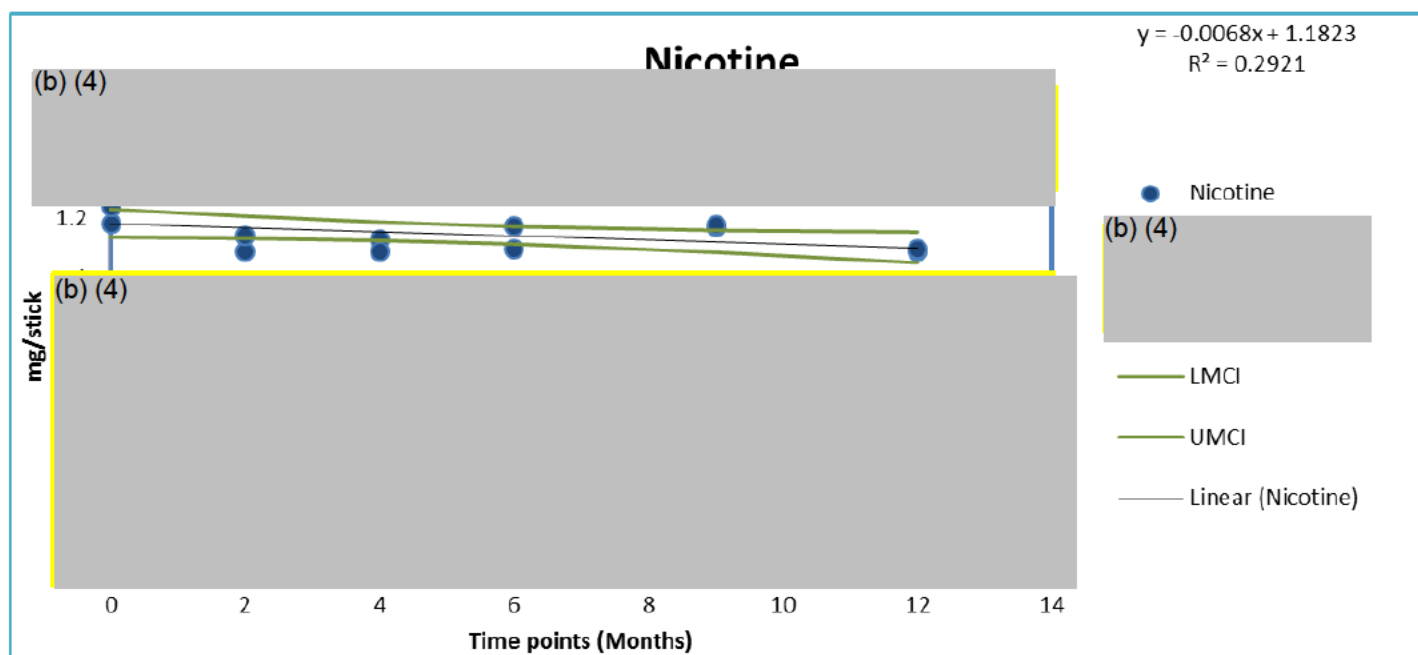


Figure 16 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.



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6.2.1.2 Glycerin

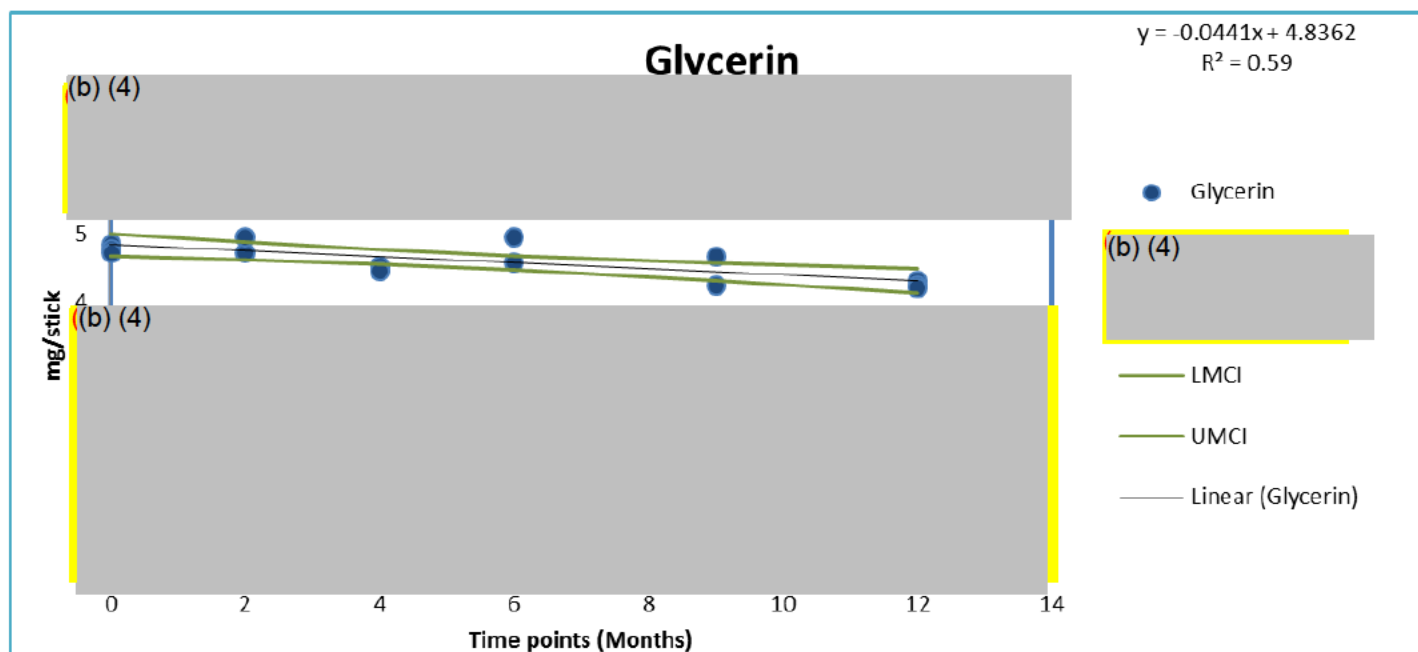


Figure 17 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.



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6.2.1.3 CO

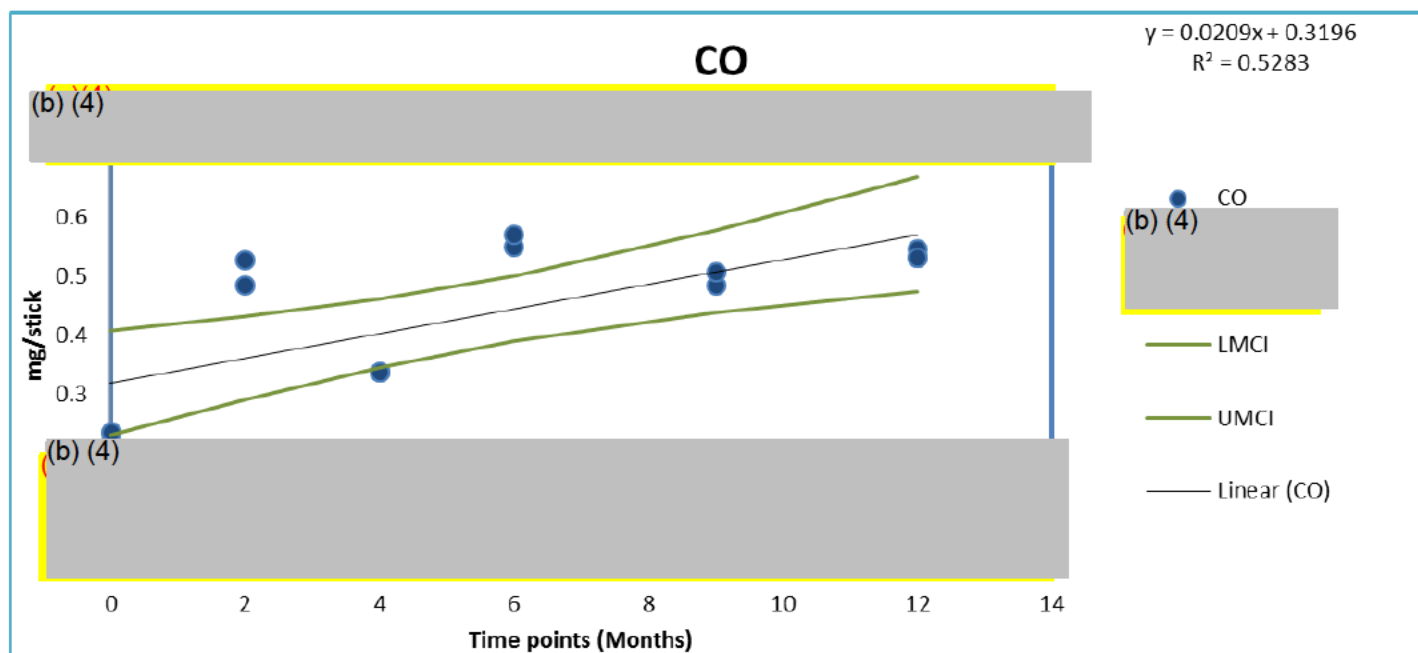


Figure 18 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.



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Form Effective Date: See EDMS

6.2.1.4 Triacetin

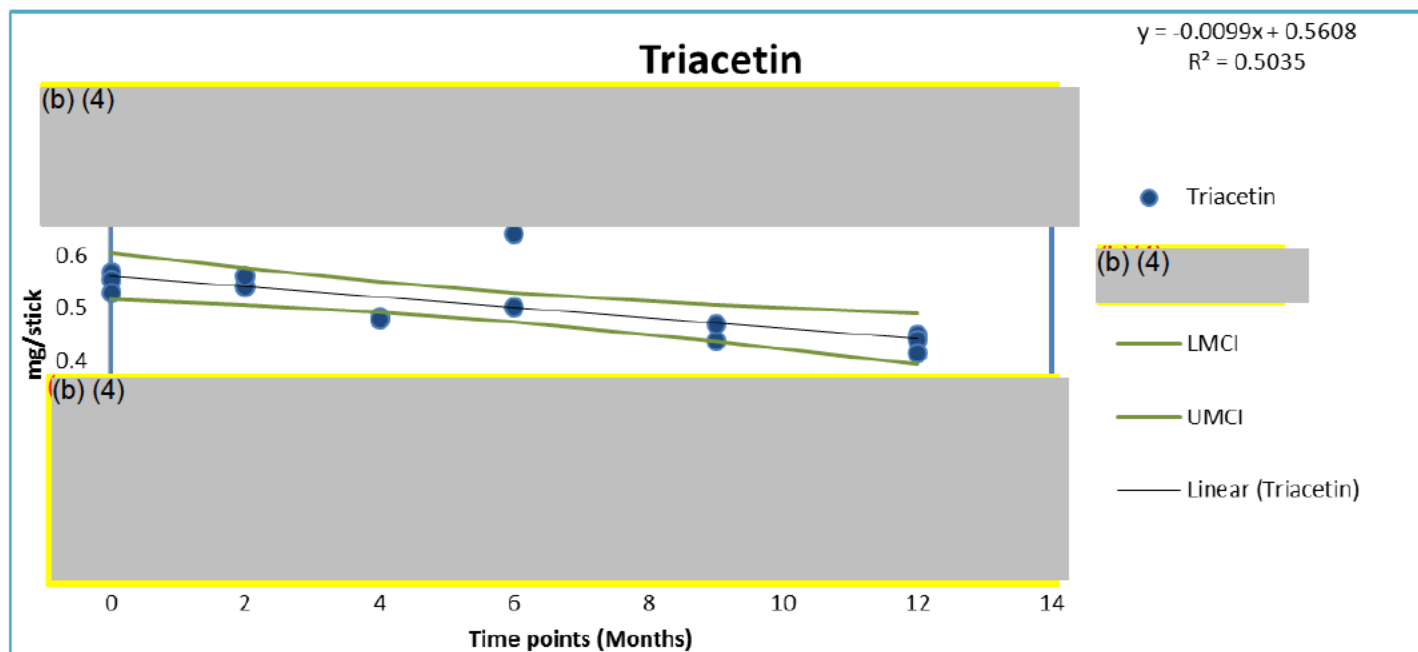


Figure 19 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.



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Form Effective Date: See EDMS

6.2.1.5 TPM

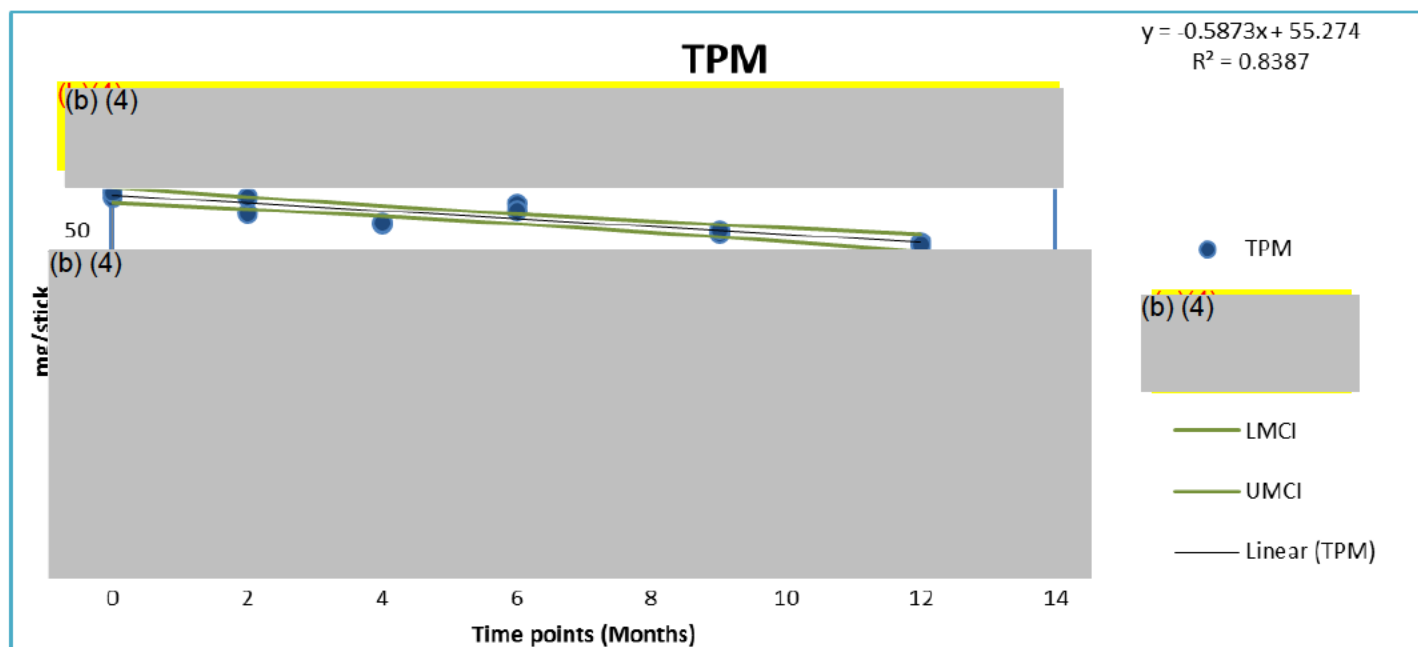


Figure 20 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.



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6.2.1.6 Phenol

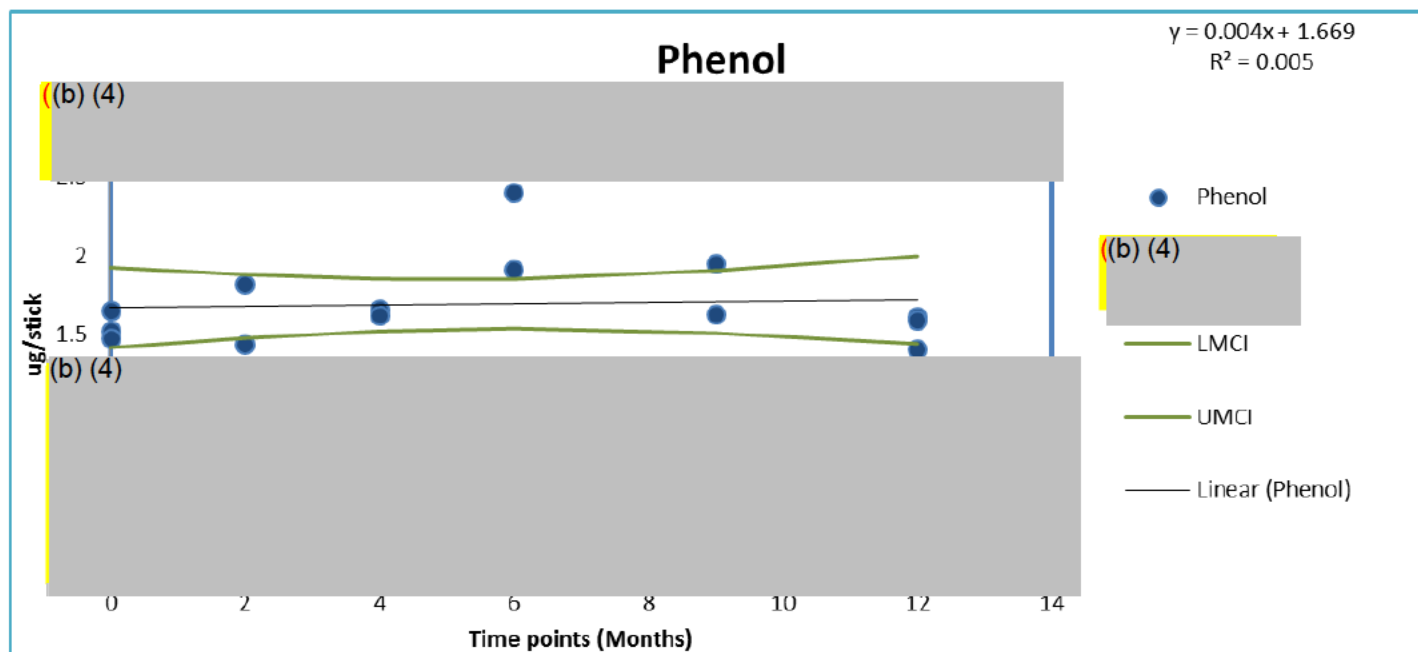


Figure 21 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.



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Form Effective Date: See EDMS

6.2.1.7 Acrylamide

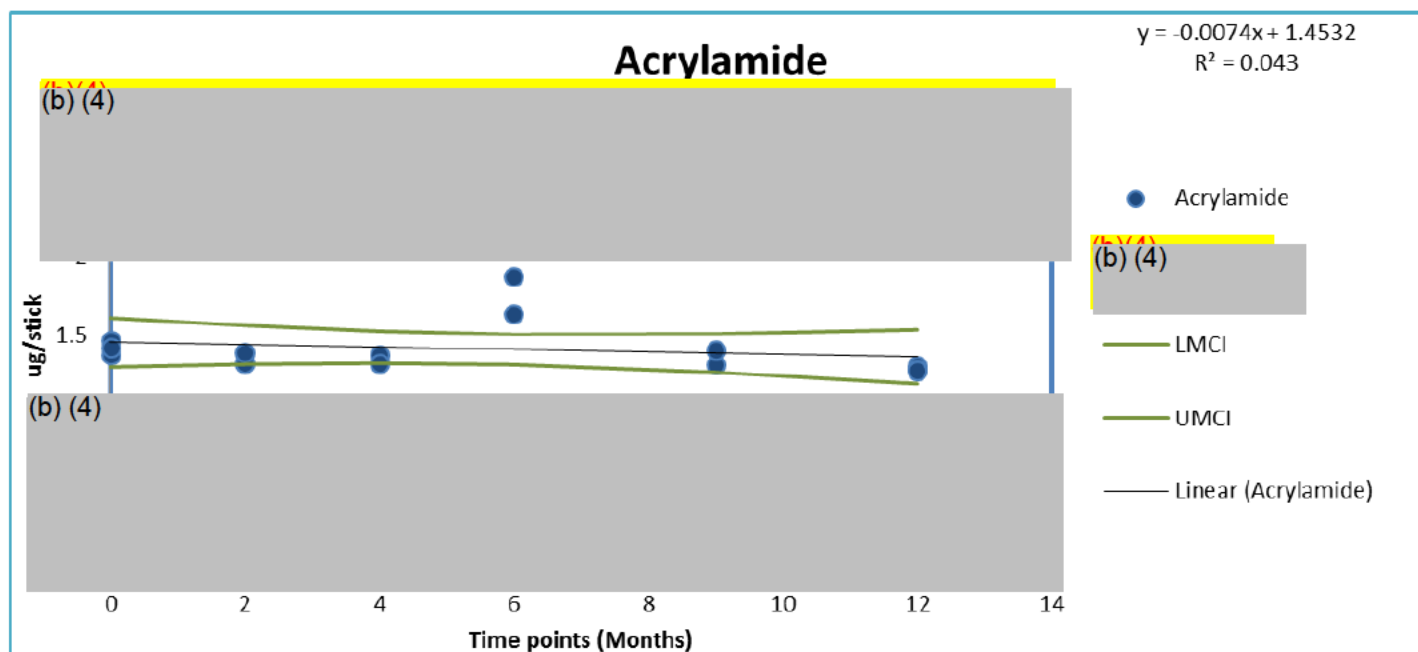


Figure 22 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.



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6.2.1.8 Acetamide

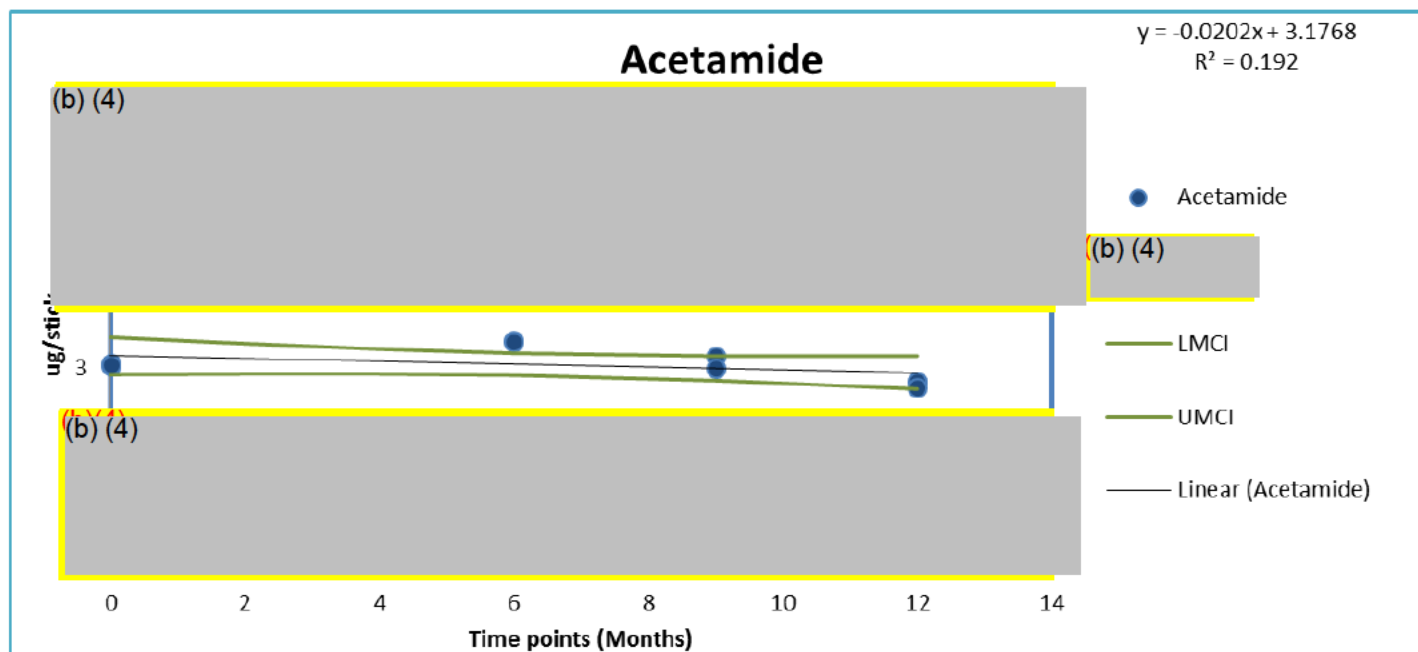


Figure 23 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.



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6.2.1.9 Acetaldehyde

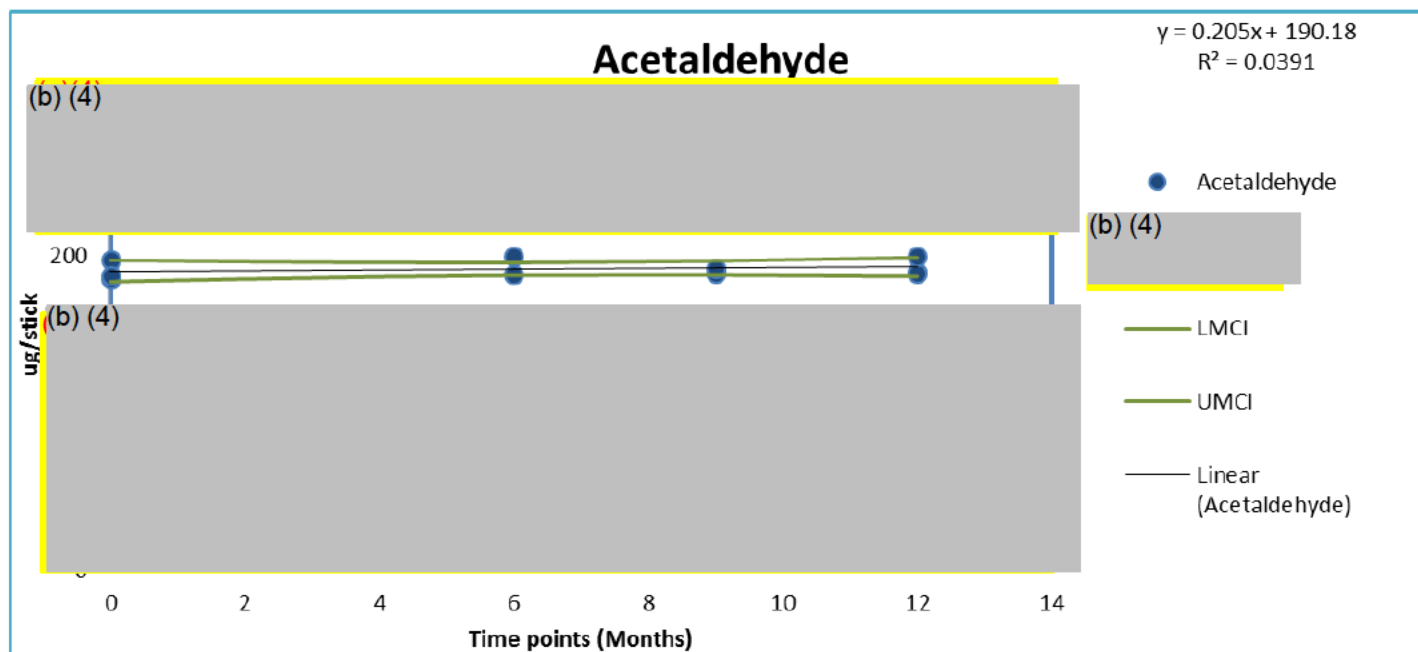


Figure 24 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.



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6.2.1.10 Butyraldehyde

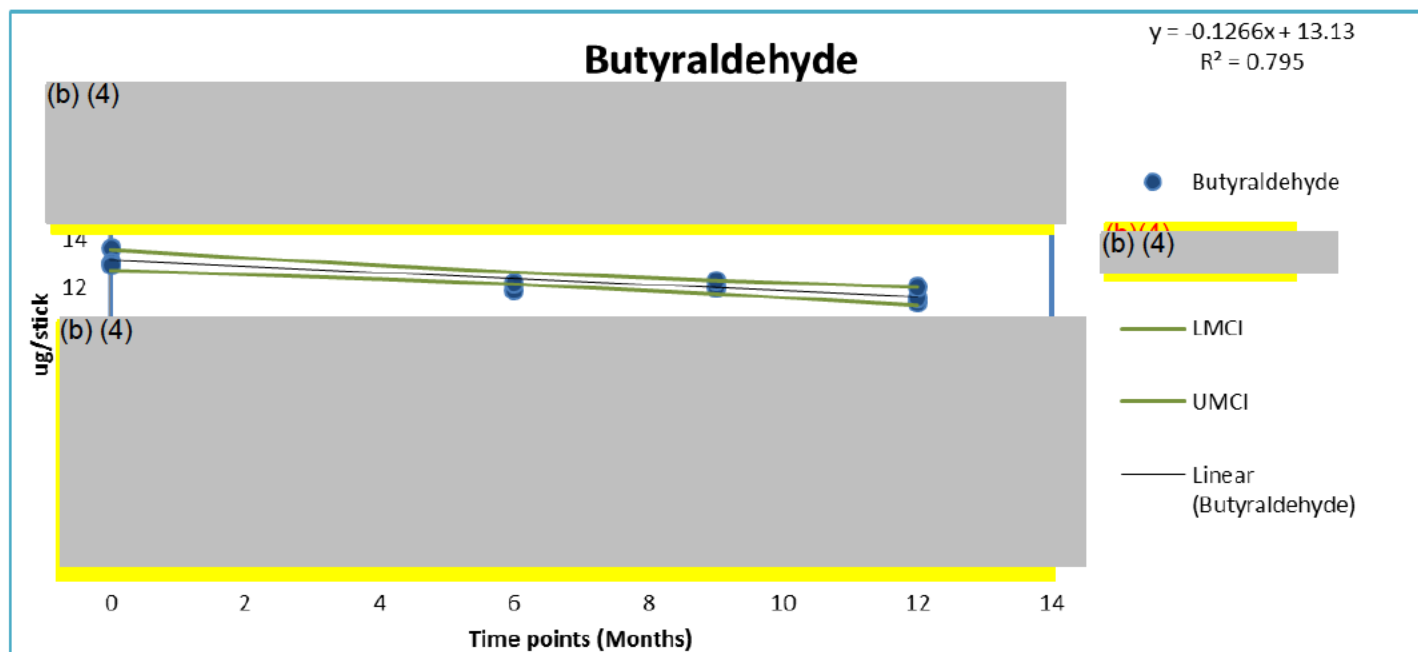


Figure 25 The best model accepted at the significance level of 0.25 has Different intercepts and Different slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.



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6.2.1.11 Acrylonitrile

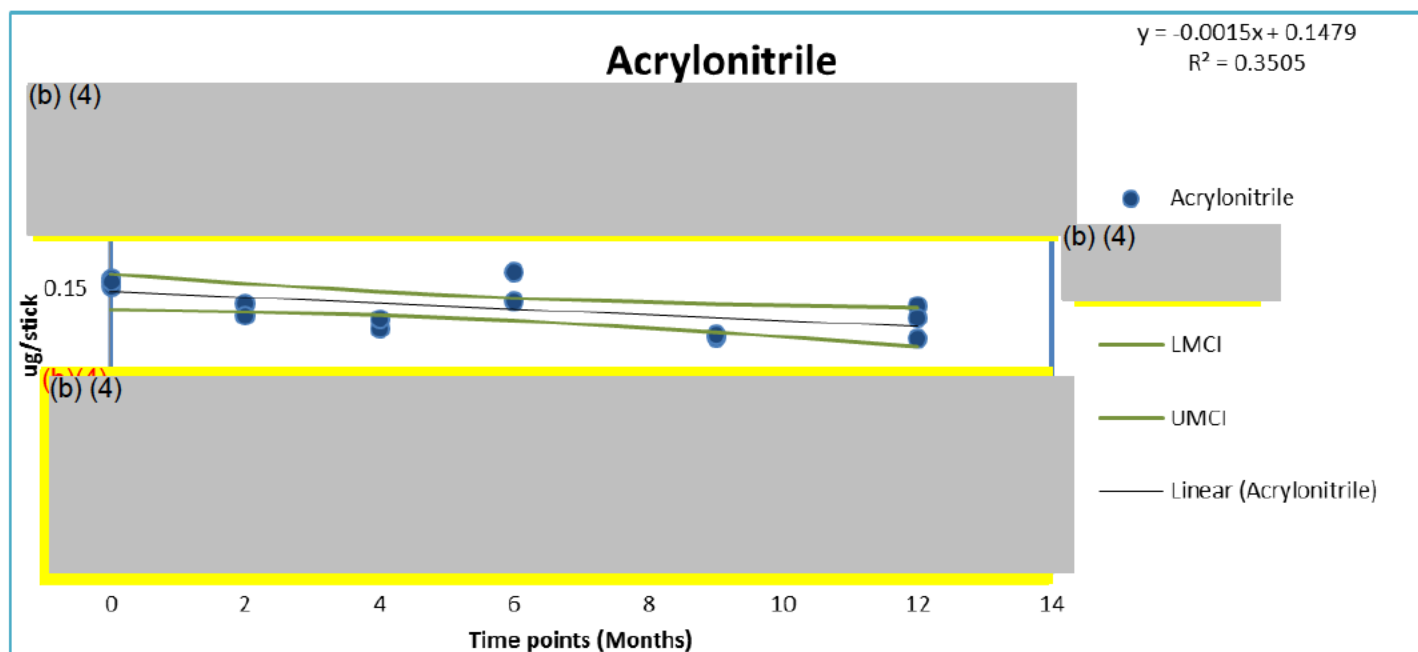


Figure 26 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.



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6.2.1.12 Isoprene

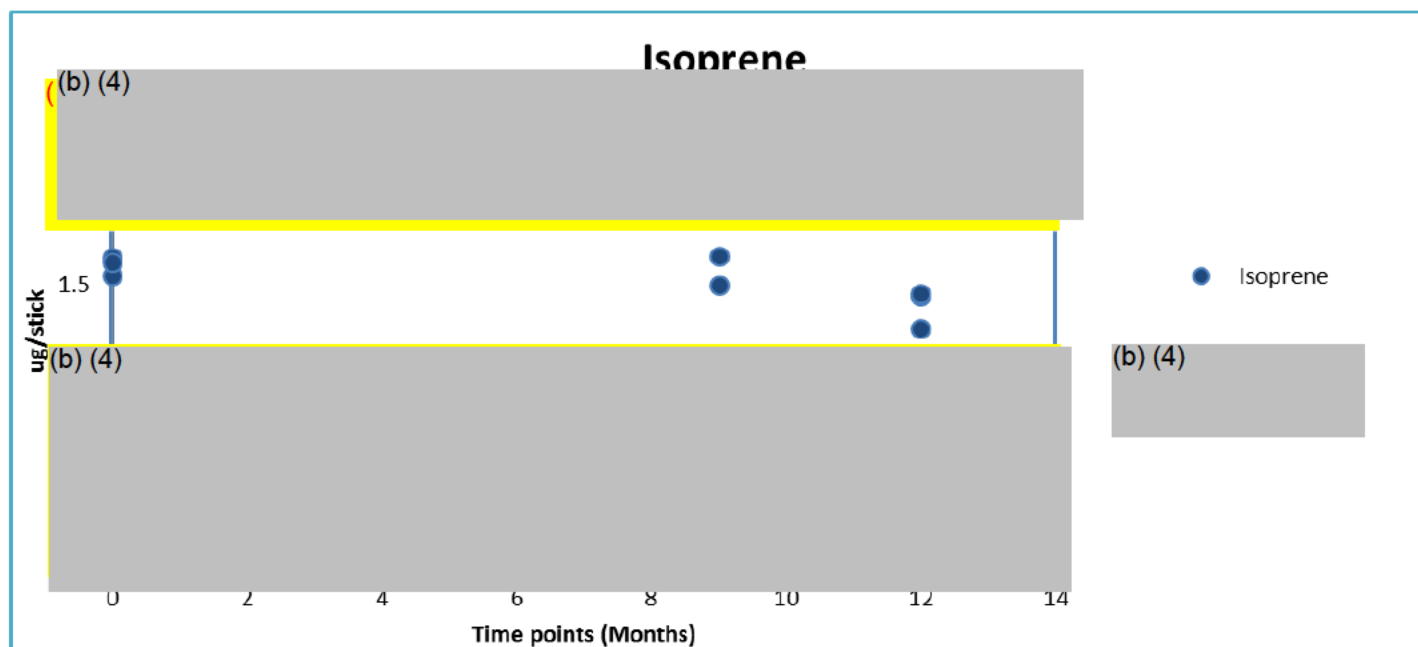


Figure 27 There is no obvious change over time in Isoprene level and all the values are well inside the specifications, therefore Isoprene is considered stable for 12 months.



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6.2.1.13 Pyridine

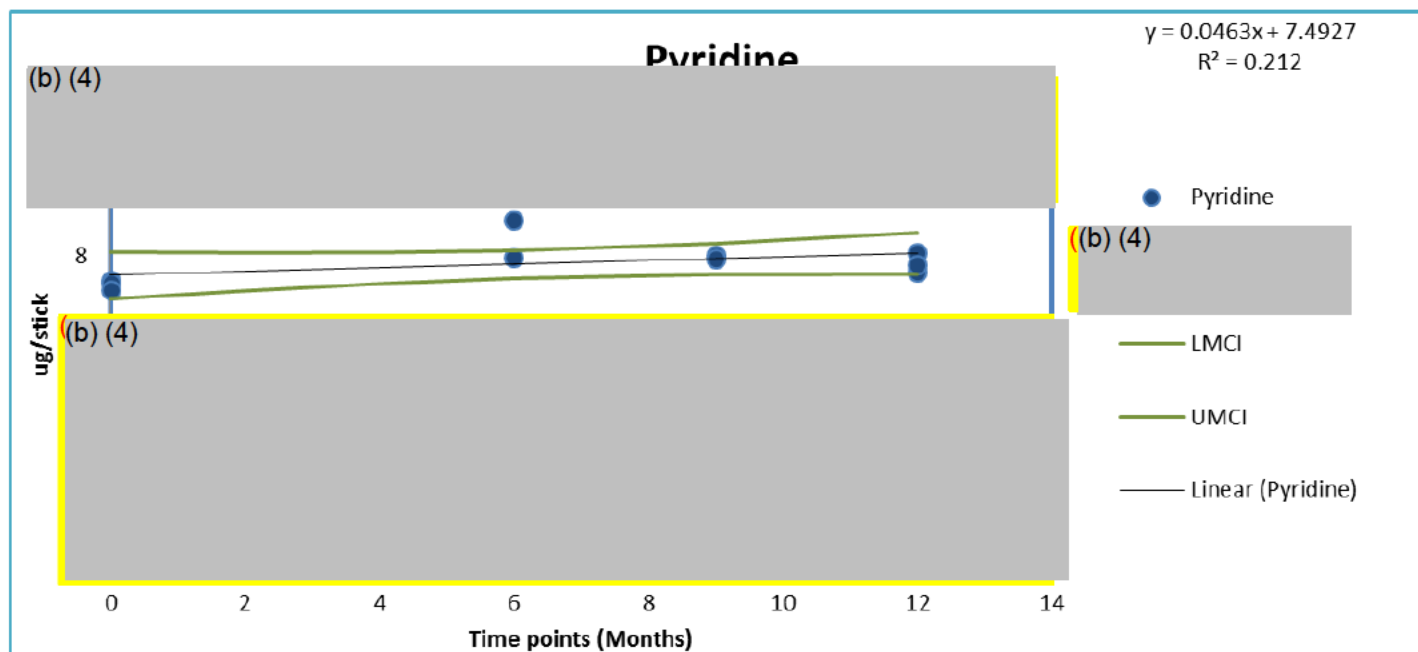


Figure 28 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months.



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Form Status: Effective
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6.2.1.14 Ammonia

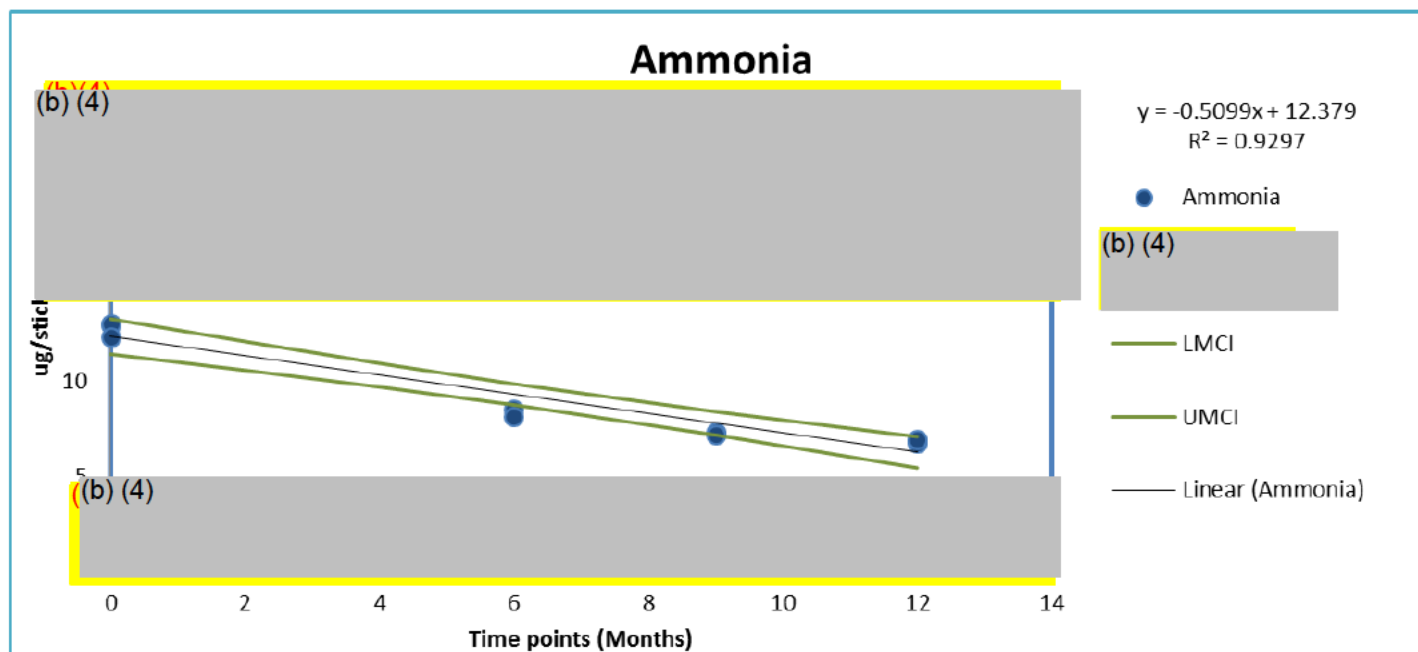


Figure 29 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 12 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 12 months

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(b) (4)





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6.2.3 Sensorial Evaluation

Sensorial evaluation results are described in details in a separate report [\[5\]](#).

(b) (4)

. As no drastic sensory changes were observed over the storage time, it is hypothesized that consumers should not reject the product for a period up to 12 months.

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

6.2.4 Visual inspection

(b) (4)

The visual quality of the tobacco sticks was found acceptable from visual point of view after 9 months of storage, however they were considered not acceptable after 12 months of storage in 30°C 35%RH.



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Form Status: Effective

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6.3 Storage Condition 30°C 75% RH

Table 11 B-25904 / 41-2397948 at 30°C 75% RH

B-25904 / 41-2397948	Unit	Specifications	Time Points (Months)						Degradation Rate	R ²	Severity Score
Test		(b) (4)	0	2	4	6	9	12			
Nicotine	mg/stick	(b) (4)	1.25	1.14	1.16				-2.00%	0.61	1.2
Glycerin	mg/stick	(b) (4)	4.9	4.9	4.6				-1.42%	0.62	0.9
CO	mg/stick	(b) (4)	0.2	0.5	0.3				6.66%	0.10	0.7
Triacetin	mg/stick	(b) (4)	0.6	0.5	0.4				-6.08%	0.95	5.8
Phenol	µg/stick	(b) (4)	1.7	1.7	1.8				2.87%	1.00	2.9
Acrylamide	µg/stick	(b) (4)	1.5	1.4	1.5				0.11%	0.03	0.0
Acetamide	µg/stick	(b) (4)	3.1						NA	NA	NA
Acetaldehyde	µg/stick	(b) (4)	197						NA	NA	NA
Butyraldehyde	µg/stick	(b) (4)	13.7						NA	NA	NA
Acrylonitrile	µg/stick	(b) (4)	0.16	0.16	0.13				-4.35%	0.72	3.1
Isoprene	µg/stick	(b) (4)	1.65	1.99*	1.70*				NA	NA	NA
Pyridine	µg/stick	(b) (4)	7.4						NA	NA	NA
Ammonia	µg/stick	(b) (4)	13.0						NA	NA	NA
TPM	mg/stick	(b) (4)	56	55	52				-1.70%	0.98	1.7

* Isoprene values in T2 and T4 are explained in [Chapter 5.2](#).



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Form Status: Effective

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Table 12 B-25905 / 41-2397950 at 30°C 75% RH

B-25905 / 41-2397950	Unit	Specifications	Time point (Months)						Degradation Rate	R ²	Severity Score
		(b) (4)	0	2	4	6	9	12			
Test											
Nicotine	mg/stick		1.18	1.16		1.12			-0.87%	1.00	0.9
Glycerin	mg/stick		4.8	5.0		4.6			-0.70%	0.32	0.2
CO	mg/stick		0.2	0.5		0.5			12.83%	0.51	6.6
Triacetin	mg/stick		0.6	0.5		0.5			-1.46%	0.88	1.3
Phenol	µg/stick		1.5	1.7		2.1			6.88%	1.00	6.9
Acrylamide	µg/stick		1.4	1.5		1.7			3.87%	1.00	3.9
Acetamide	µg/stick		3.0			3.7			NA	NA	NA
Acetaldehyde	µg/stick		185			213			NA	NA	NA
Butyraldehyde	µg/stick		13.0			12.6			NA	NA	NA
Acrylonitrile	µg/stick		0.15	0.15		0.13			-2.65%	0.94	2.5
Isoprene	µg/stick		1.55	1.72*		1.63*			NA	NA	NA
Pyridine	µg/stick		7.3			7.6			NA	NA	NA
Ammonia	µg/stick		13.0			9.7			NA	NA	NA
TPM	ma/stick		55	55		52			-0.90%	0.89	0.8

* Isoprene values in T2 and T4 are

explained in [Chapter 5.2](#).



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Table 13 B-25906 / 41-2382704 at 30°C 75% RH

B-25906 / 41-2382704	Unit	Specifications	Time Points (Months)						Degradation Rate	R ²	Severity Score
Test		(b) (4)	0	2	4	6	9	12			
Nicotine	mg/stic	(b) (4)	1.24		1.14	1.17			-1.09%	0.62	0.7
Glycerin	mg/stic		4.7		4.9	4.8			0.47%	0.49	0.2
CO	mg/stic		0.2		0.3	0.6			24.56%	0.84	20.6
Triacetin	mg/stic		0.5		0.5	0.5			0.06%	0.00	0.0
Phenol	µg/stick		1.5		2.3	2.3			9.30%	0.90	8.4
Acrylamide	µg/stick		1.4		1.5	1.8			4.10%	0.63	2.6
Acetamide	µg/stick		3.1			3.5			NA	NA	NA
Acetaldehyde	µg/stick		187			197			NA	NA	NA
Butyraldehyde	µg/stick		13.0			11.8			NA	NA	NA
Acrylonitrile	µg/stick		0.15		0.14	0.15			-0.81%	0.16	0.1
Isoprene	µg/stick		1.62		1.72*	1.96*			NA	NA	NA
Pyridine	µg/stick		7.1			7.8			NA	NA	NA
Ammonia	µg/stick		12.3			9.5			NA	NA	NA

(b) (4)

* Isoprene values in T2 and T4 are explained in [Chapter 5.2](#).



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6.3.1 Mainstream Aerosol Evaluation

6.3.1.1 Nicotine

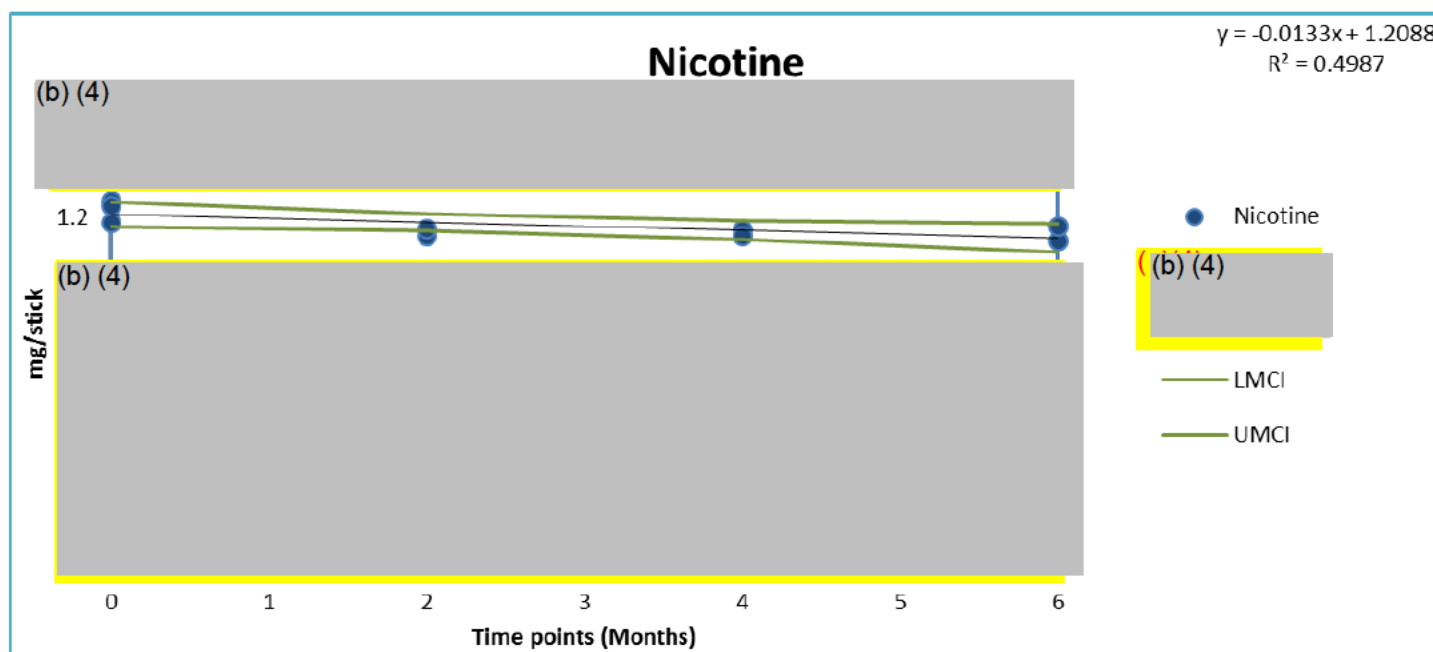


Figure 31 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 6 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 6 months.



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Form Status: Effective
Form Effective Date: See EDMS

6.3.1.2 Glycerin

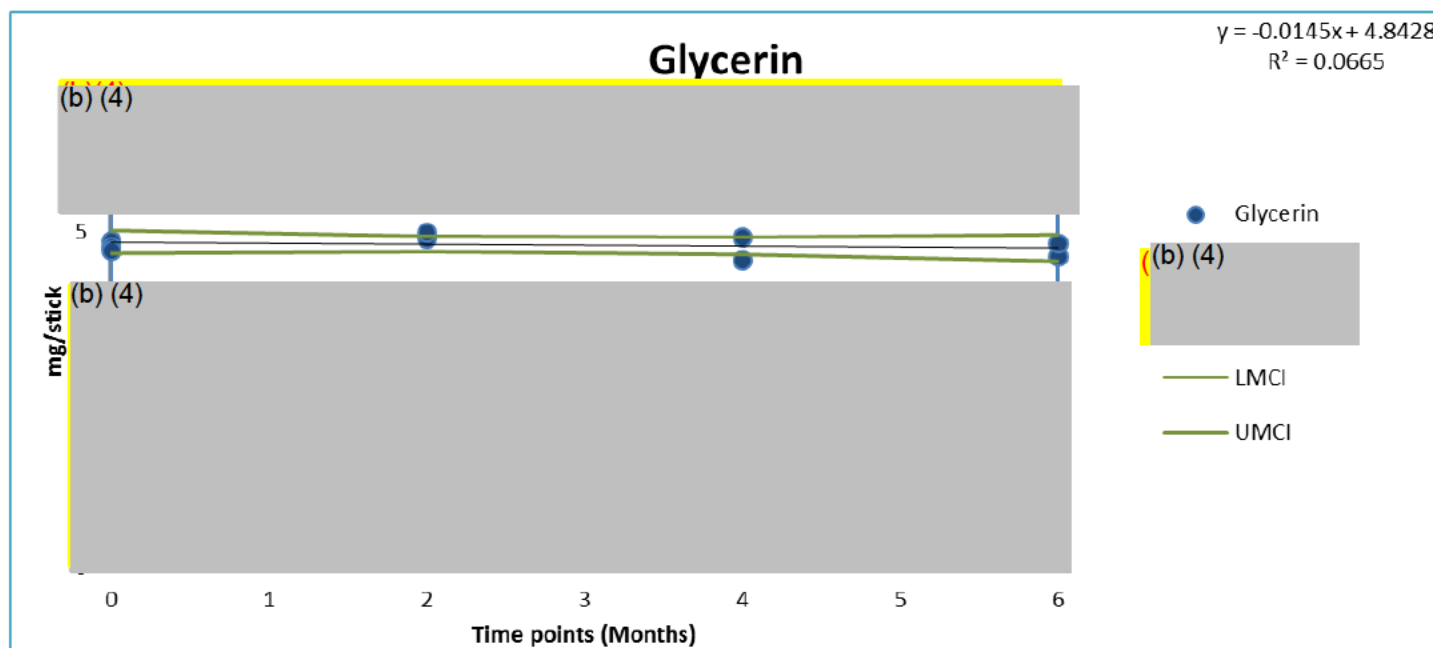


Figure 32 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 6 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 6 months.



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6.3.1.3 CO

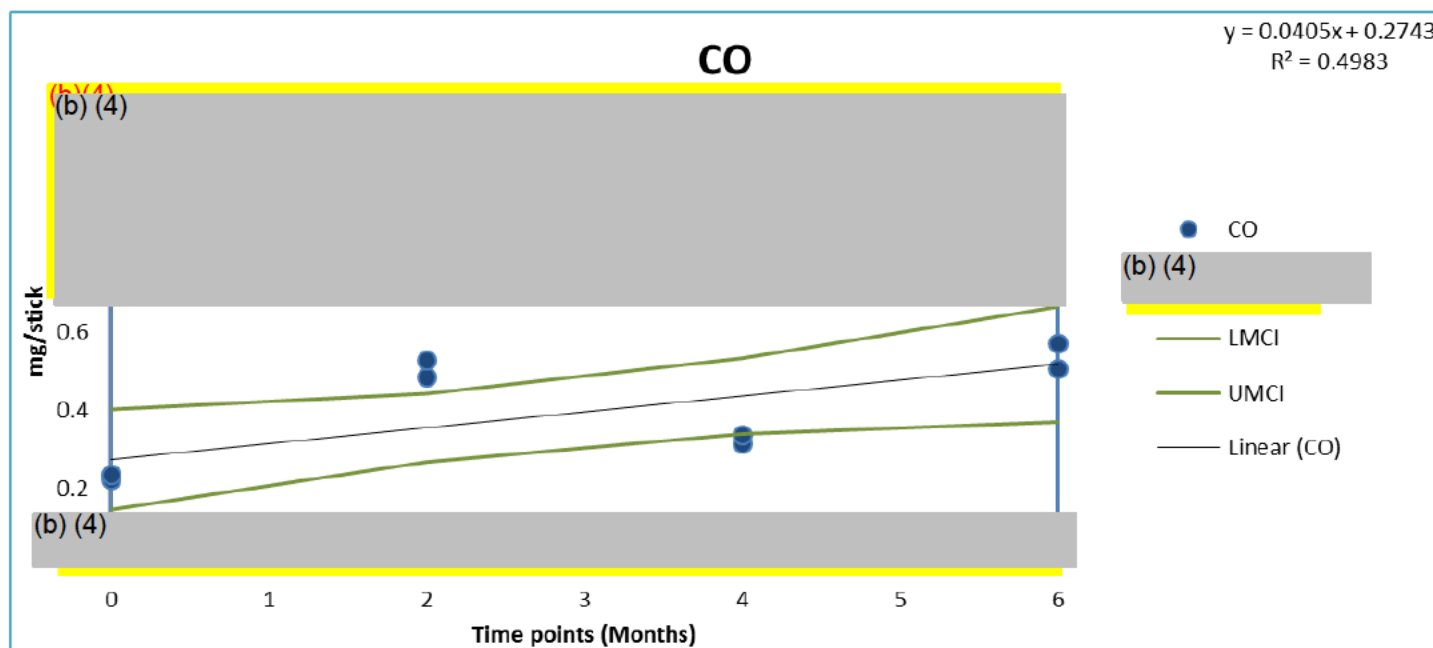


Figure 33 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time at 6 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 6 months.



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Form Status: Effective
Form Effective Date: See EDMS

6.3.1.4 Triacetin

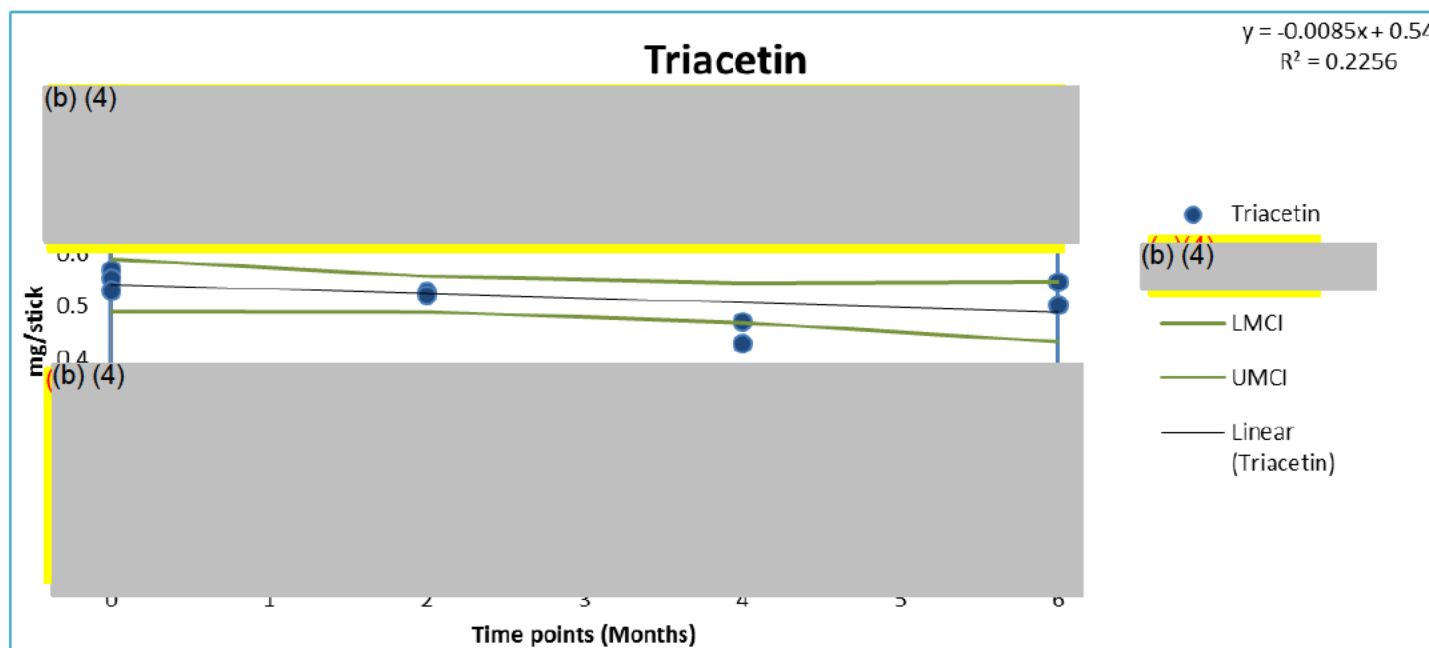


Figure 34 There is no obvious trend over time in Triacetin level and all the values are well inside the specifications, therefore Triacetin is considered stable for 6 months.



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Form Status: Effective
Form Effective Date: See EDMS

6.3.1.5 TPM

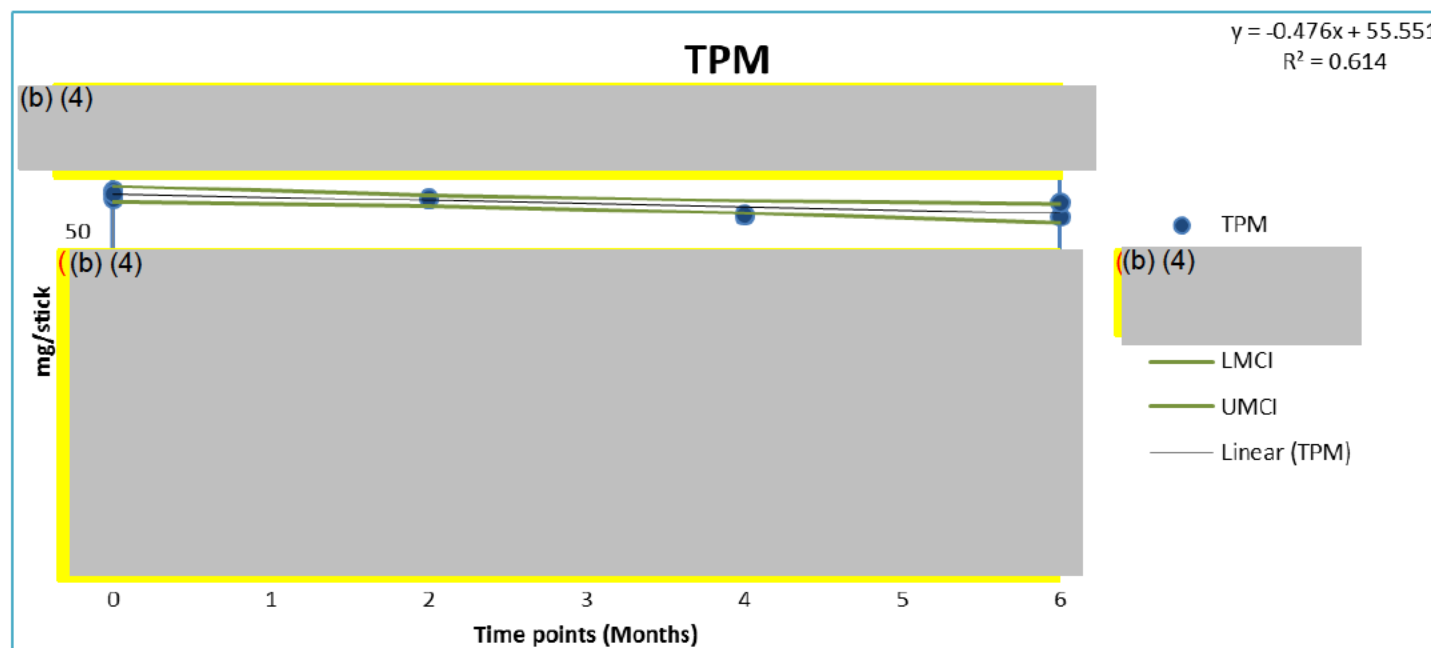


Figure 35 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 6 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 6 months.



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6.3.1.6 Phenol

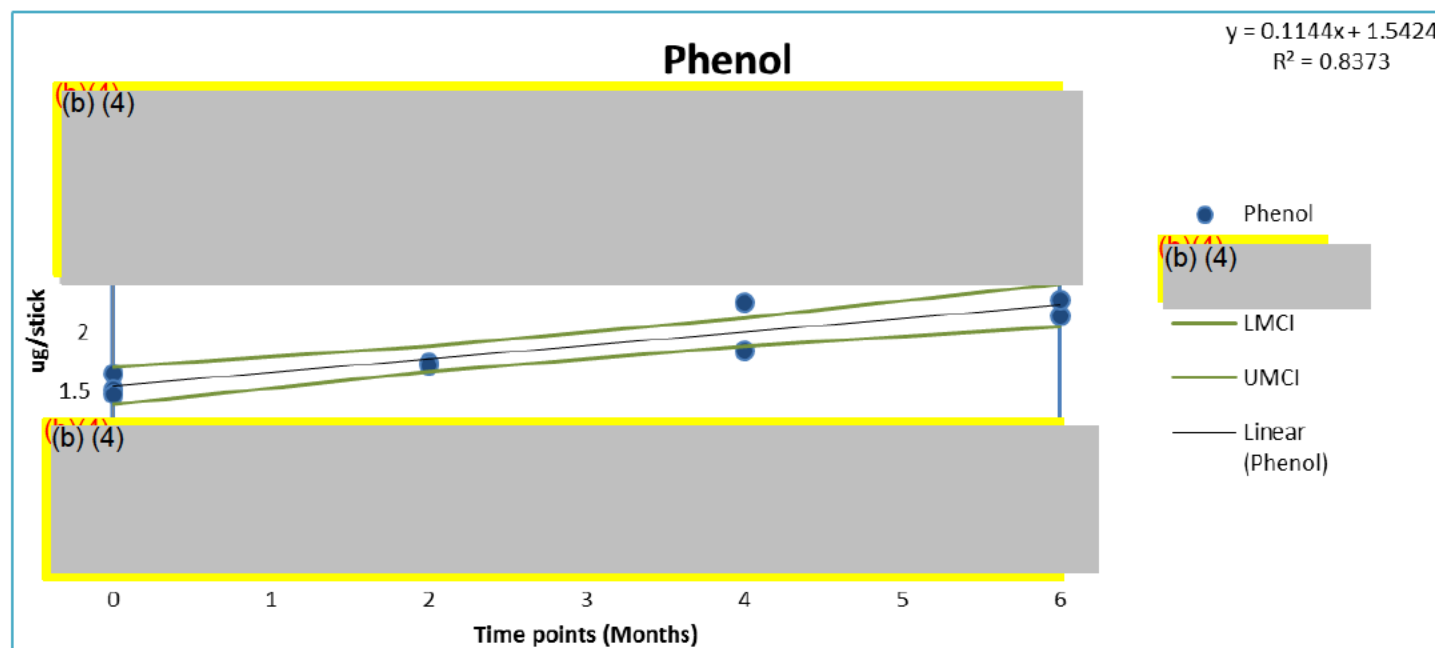


Figure 36 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time at 6 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 6 months.



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6.3.1.7 Acrylamide

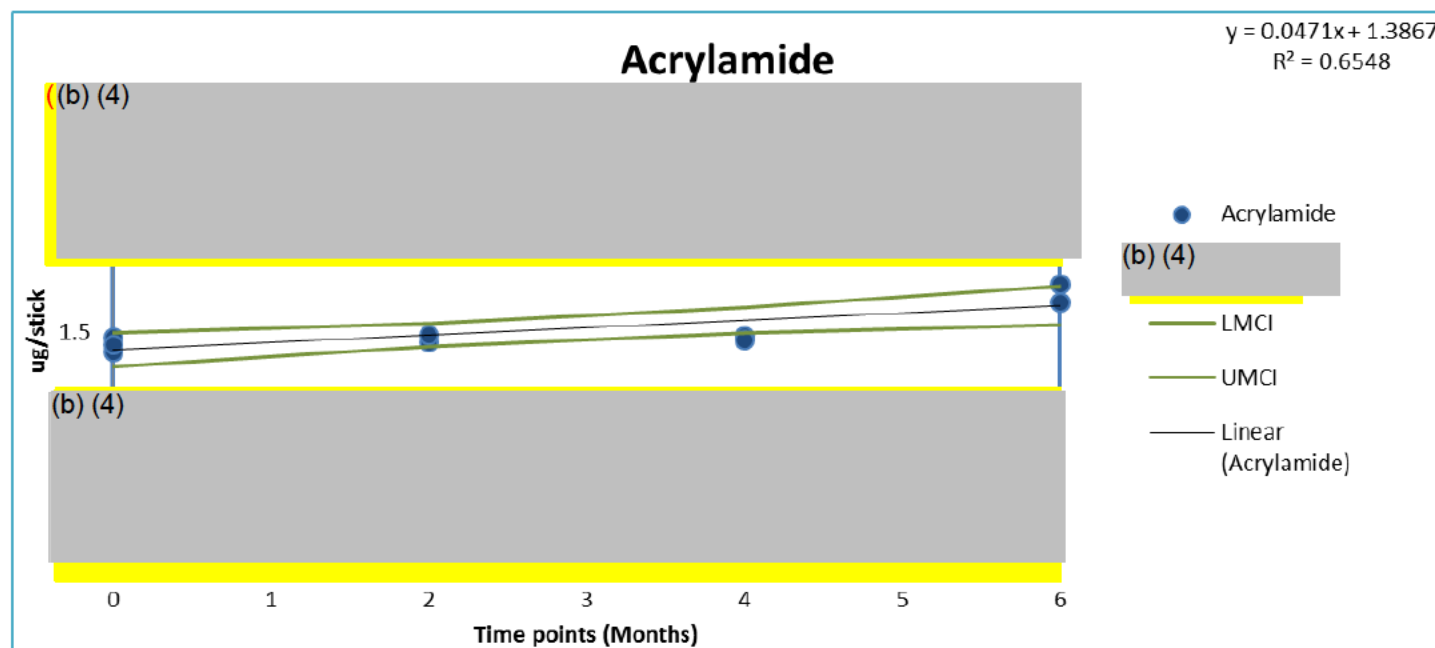


Figure 37 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 6 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 6 months.



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Form Status: Effective
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6.3.1.8 Acetamide

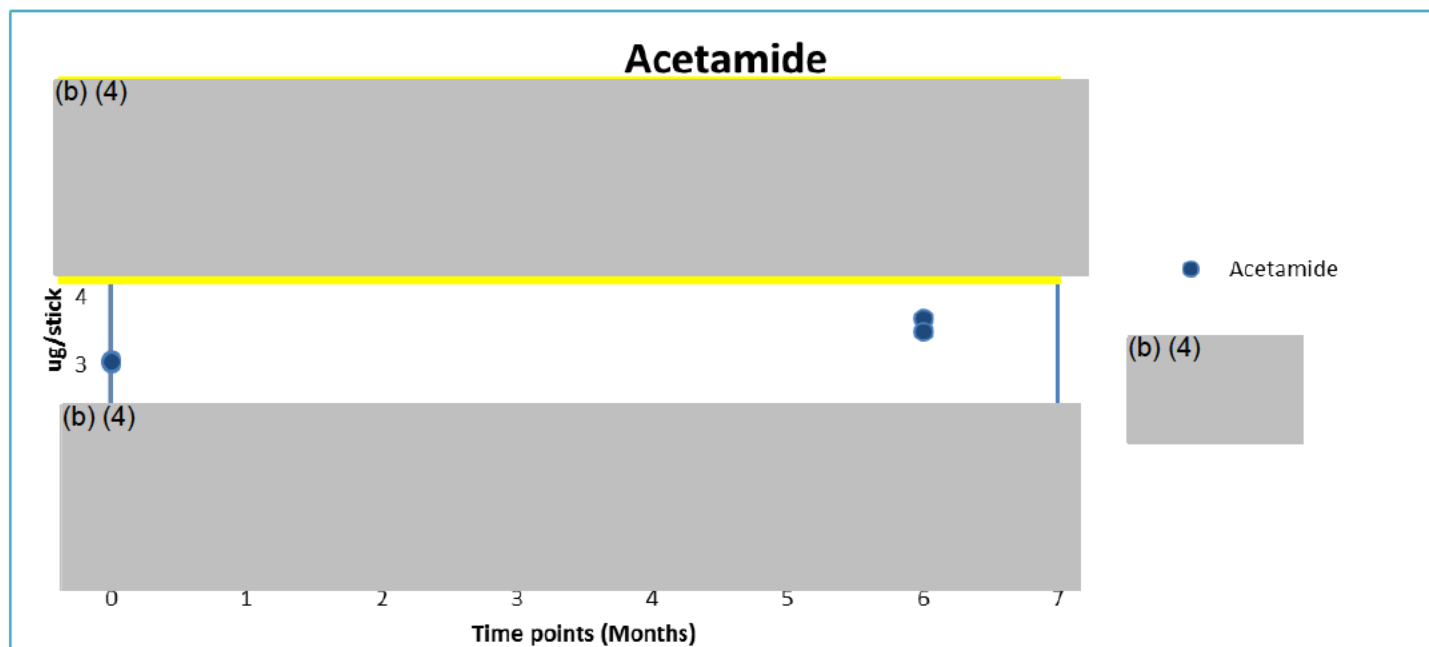


Figure 38 Acetamide is not suitable for trend analysis since it was tested in less than 3 different time points. All the values obtained are inside the specifications and therefore Acetamide is considered stable for 6 months.



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Form Status: Effective
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6.3.1.9 Acetaldehyde

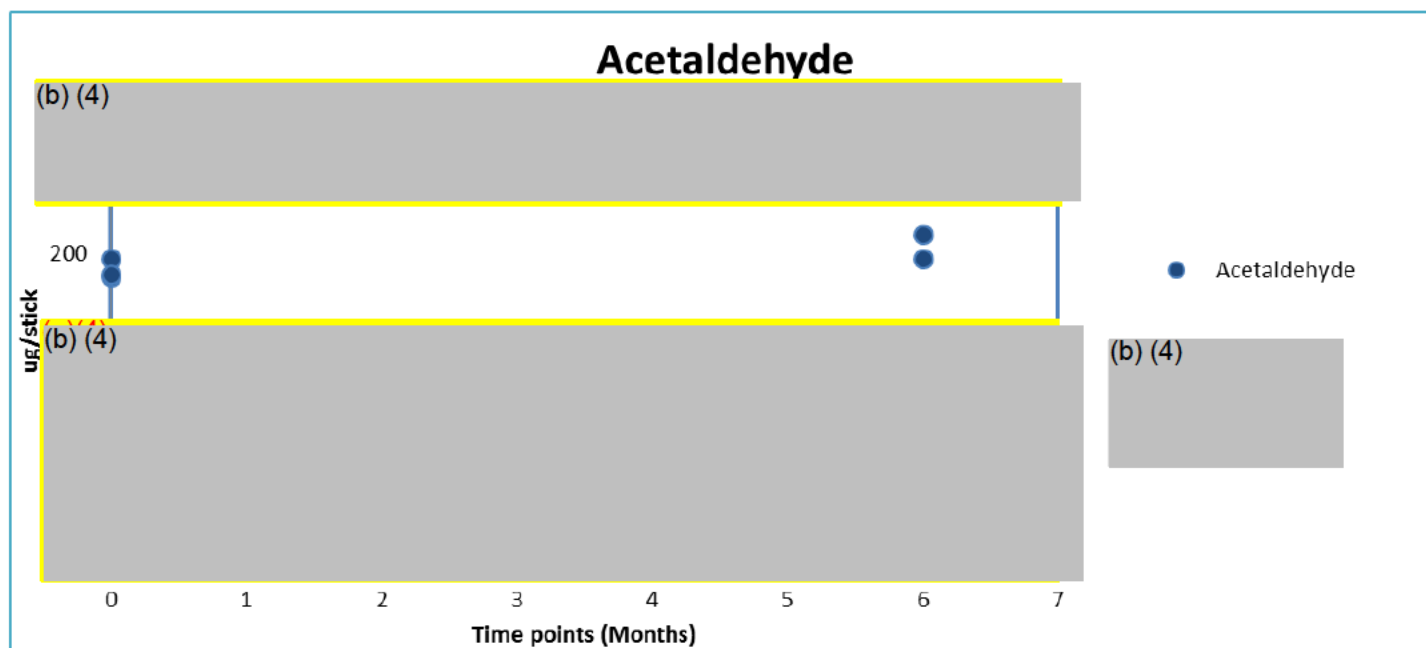


Figure 39 Acetaldehyde is not suitable for trend analysis since it was tested in less than 3 different time points. All the values obtained are inside the specifications and therefore Acetaldehyde is considered stable for 6 months.



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Form Status: Effective
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6.3.1.10 Butyraldehyde

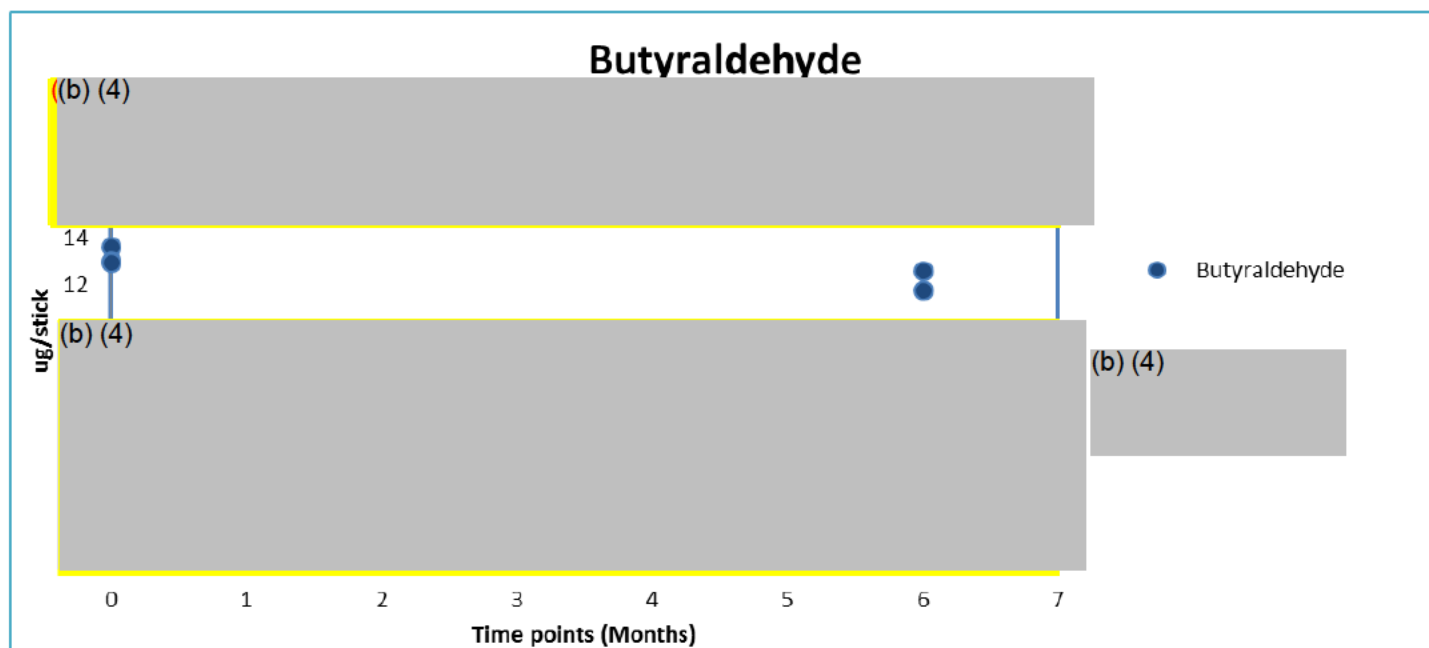


Figure 40 Butyraldehyde is not suitable for trend analysis since it was tested in less than 3 different time points. All the values obtained are inside the specifications and therefore Butyraldehyde is considered stable for 6 months.



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6.3.1.11 Acrylonitrile

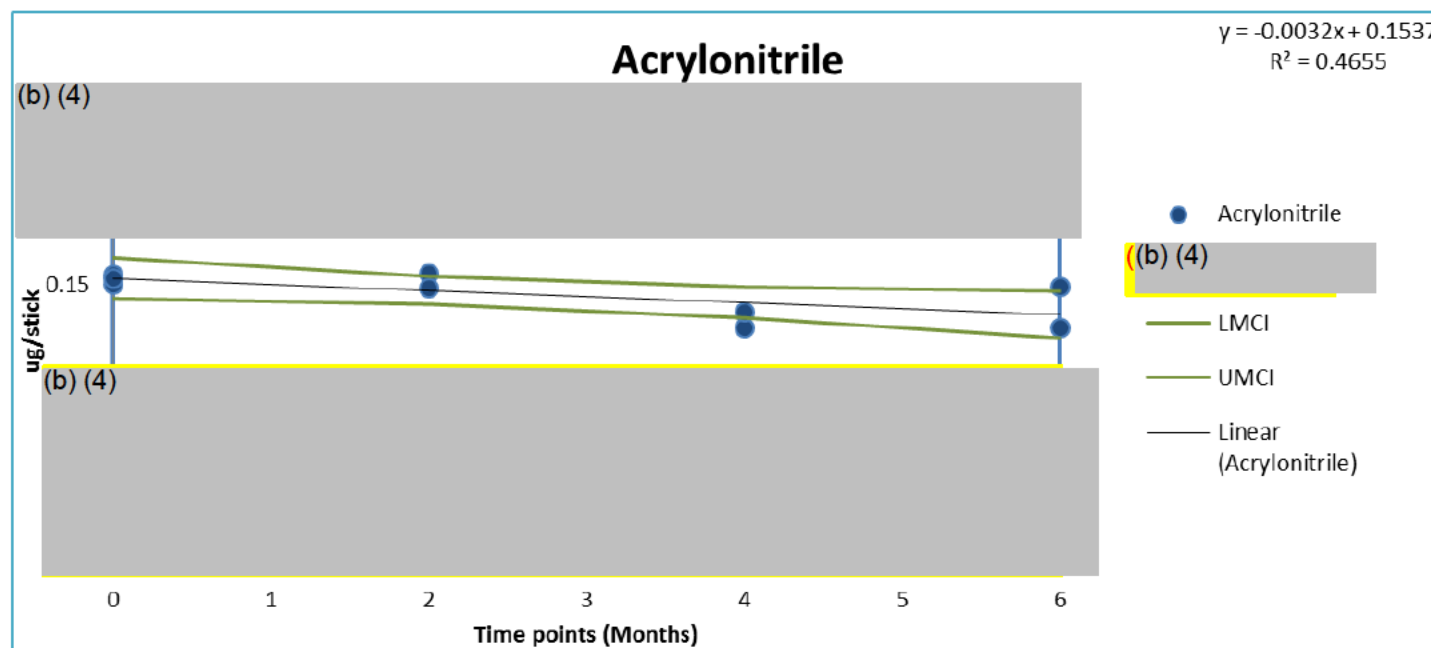


Figure 41 The best model accepted at the significance level of 0.25 has Common intercepts and Common slopes. The model suggests the earliest crossing time over 6 months with 95 percent confidence. ICH Guidelines indicate an expiration time of 6 months.



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6.3.1.12 Isoprene

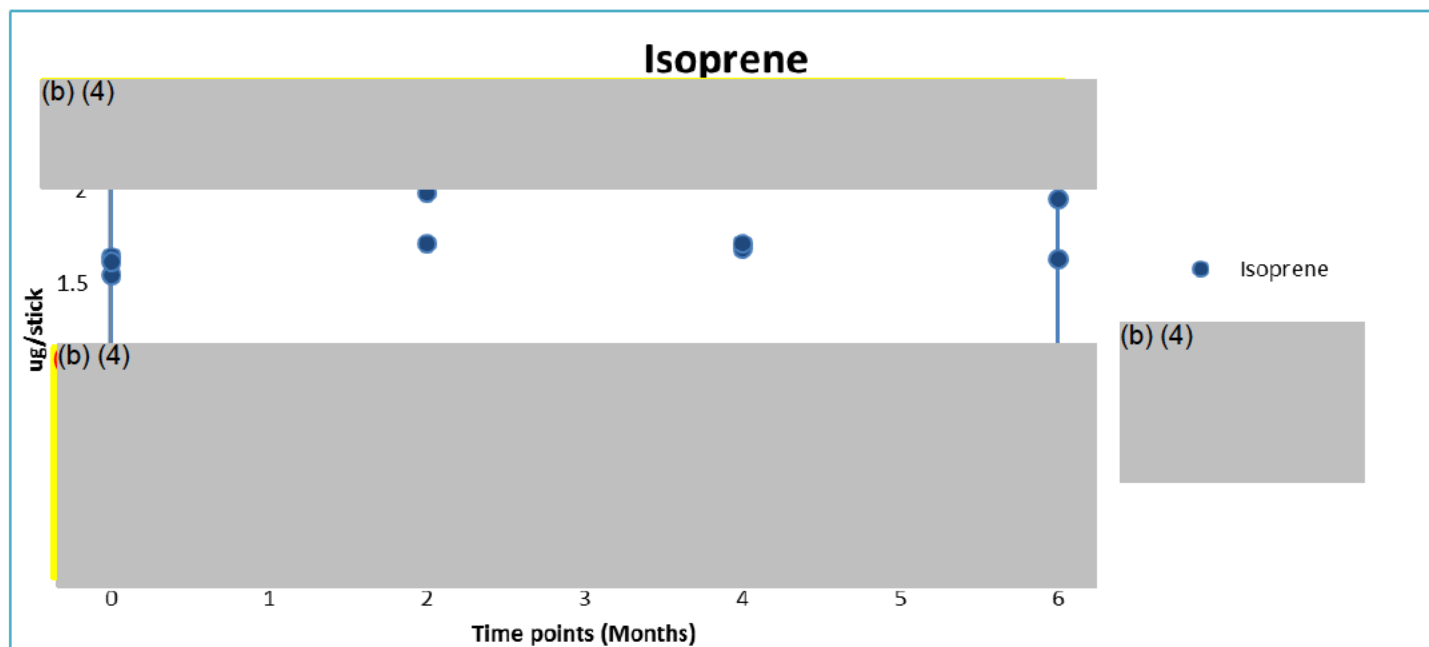


Figure 42 There is no obvious change over time in Isoprene level and all the values are well inside the specifications even with the overestimated values in T2, T4 and T6 (see [Chapter 5.2](#)), therefore Isoprene is considered stable for 6 months.



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Form Effective Date: See EDMS

6.3.1.13 Pyridine

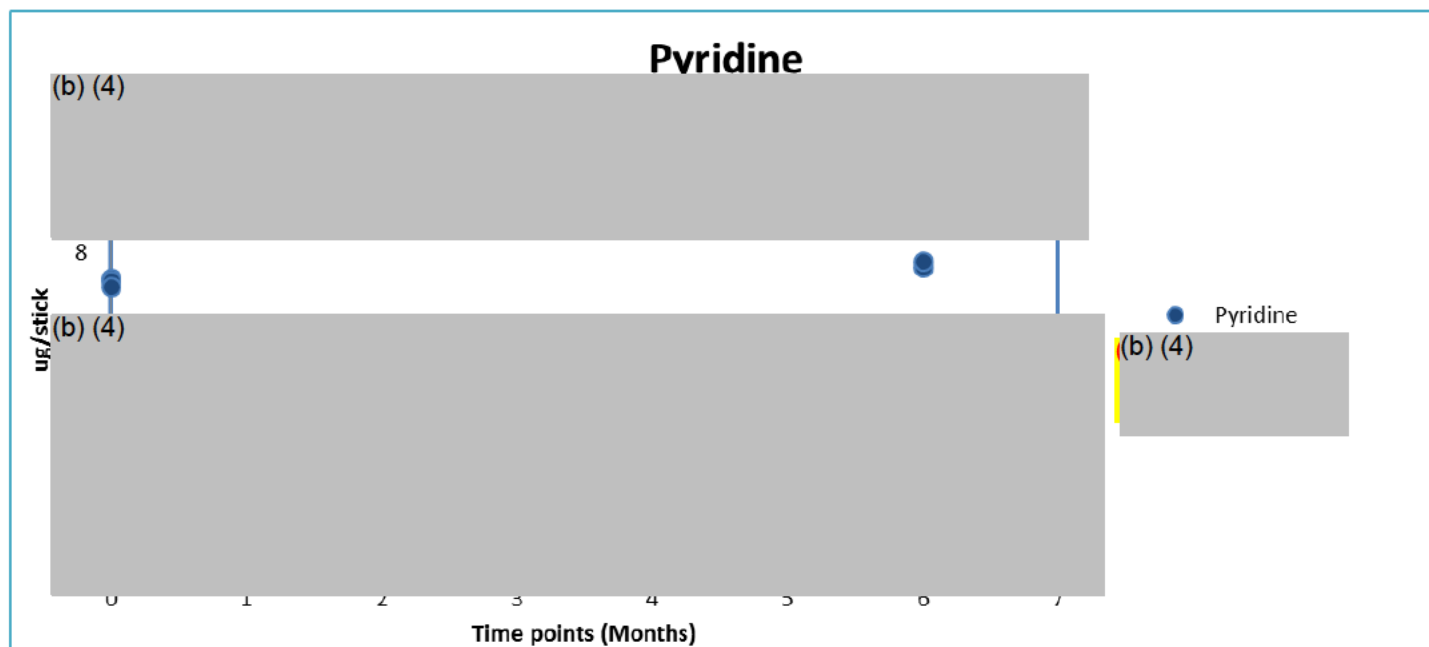


Figure 43 Pyridine is not suitable for trend analysis since it was tested in less than 3 different time points. All the values obtained are inside the specifications and therefore Pyridine is considered stable for 6 months.



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6.3.1.14 Ammonia

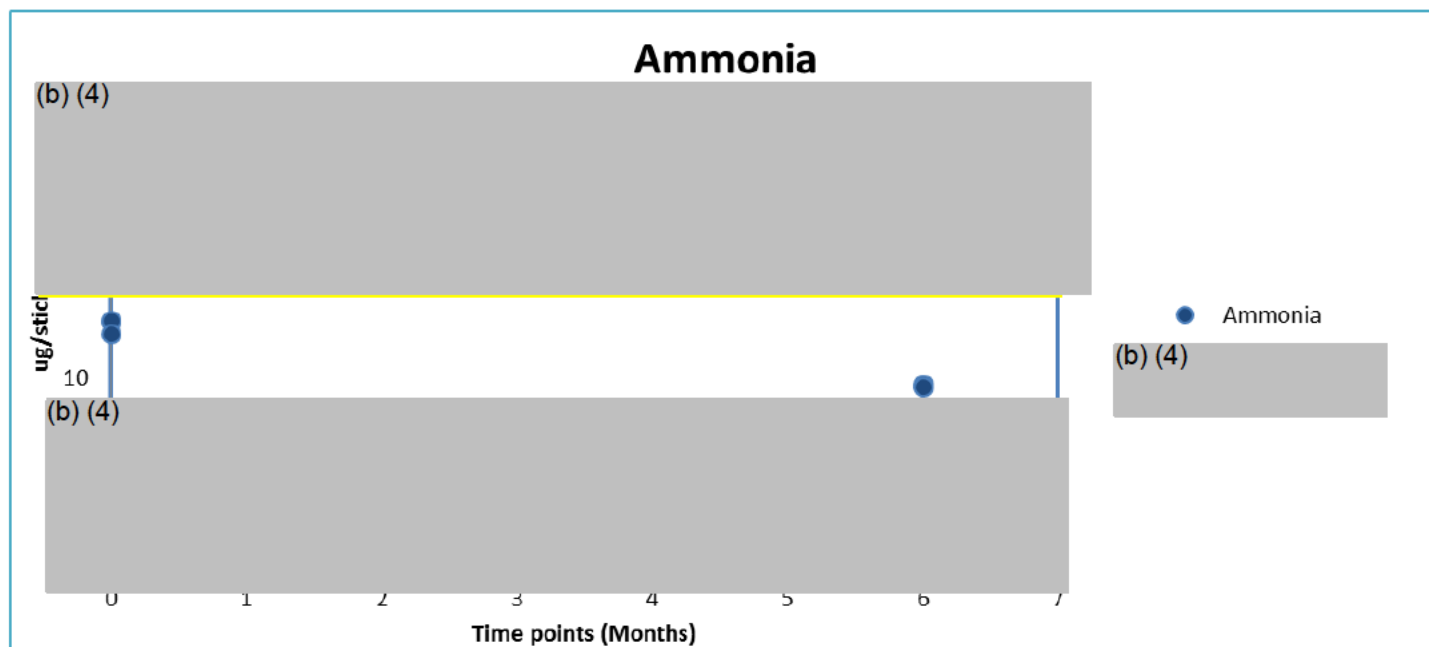


Figure 44 Ammonia is not suitable for trend analysis since it was tested in less than 3 different time points. All the values obtained are inside the specifications and therefore Ammonia is considered stable for 6 months.



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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 can be 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°C 75%RH.



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7 Stability Assessment

Overall it can be concluded that the THS 2.2 Dorado II Ron remained within specifications up to 12 months in the 22°C 60%RH and 30°C 35%RH conditions; and up to 3 months in the 30°C 75%RH.

In the conditions 22°C 60%RH all the product parameters were found stable for 12 months with the exception of:

- Visual aspect of the sticks was found acceptable until 9 months due to some discoloration of the stick paper.

In the conditions 30°C 35%RH all the product parameters were found stable for 12 months with the exception of:

- Visual aspect of the sticks was found acceptable until 9 months due to some discoloration of the stick paper.

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

- Heat Stick Diameter was stable up to 3 months
- Visual aspect was found acceptable up to 2 months.

8 Related Documents

[1] P1 THS 2 2 EXPT004923_STABILITY STUDY PROTOCOL DORADO II RON.doc

<https://disco.app.pmi/disco/drl/objectId/0901d4ec805a5ee7>

[2] P1 Product specifications

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

[3] P1_PDev_SPE_DII Ron Batch release specs.doc

<https://disco.app.pmi/disco/drl/objectId/0901d4ec8052959a>

[4] P1_PDev_SPE_DII Ron Performance Specifications.doc

<https://disco.app.pmi/disco/drl/objectId/0901d4ec80525873>

[5] P1_CPD_SWP_Product monitoring_SS_006_2017_02_2_MRTP_DII Ron_T12

<http://rrpplm.app.pmi/Agile/PLMServlet?fromPCClient=true&module=ActivityHandler&requestUrl=module%3DActivityHandler%26opcode%3DdisplayObject%26classid%3D18387%26objid%3D229027%26tabid%3D%26>

[6] Scientific Report: PT_AL_Isoprene Investigation_PMI_RD_WKI_000383

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



Form Number: PMI_RD_FOR_000927

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Form Status: Effective

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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

10 Revision History for Stability Report

Version Nr	Description of change	Justification
1.0	Initial version.	NA
2.0	<ol style="list-style-type: none"> Alignment of vocabulary for specifications throughout the report. In Chapter 6 Stability Data Evaluation description was clarified regarding conclusion about shelf life and truncation. Removal of duplicated title Chapter 7 Stability Data Evaluation. Correction in Figure titles in Chapter 7 (Chapter 6 in this version) of the earliest crossing time. For all tested parameters evaluated (b) (4) 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) (4) was longer than the study length. Chapter 8 (Chapter 7 in this version) Stability Assessment has been reviewed in order to conclude about product stability parameters and removed product shelf life recommendation. Stability of Heat Stick Diameter was truncated from 3.8 to 3 months for condition 30°C 75%RH. 	<ol style="list-style-type: none"> Clarification that the specifications used are the product specifications. This is a clarification about how data evaluation was done and reported. Chapter 6 and 7 had the same title (Stability Data Evaluation). The earliest crossing time was wrongly written for attributes where the (b) (4) model determined earliest crossing time longer than the study duration. The decision about product shelf life remains to the sponsor of the study. Truncation of stability for Heat Stick Diameter was aligned with the description in the Data Evaluation chapter.

11 Definitions and Abbreviations

Abbreviation	
CO	Carbon Monoxide
IP	Intermediate Precision



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Abbreviation	
ISO	International Organization for Standardization
LMCI	95% lower mean confidence interval for the predicted values
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-10637, TO-10639, TO-10640	RLS-ZRH-2016-30/31
T2	TO-10980, TO-10981, TO-10982	RLS-ZRH-2016-121/122
T4	TO-11420, TO-11421, TO-11422	RLS-ZRH-2016-204/205
T6	TO-11897, TO-11898, TO-11899	RLS-ZRH-2016-311/312
T9	TO-12739, TO-12740, TO-12744	RLS-ZRH-2016-455/456
T12	TO-13570, TO-13572, TO-13616	RLS-ZRH-2017-53/54