7.2.: PRODUCT ANALYSIS – STABILITY

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7.2. PRODUCT ANALYSIS – STABILITY

7.2.1. Purpose of Study

Section 911(d)(3) of the FD&C Act requires an Modified Risk Tobacco Product Application (MRTPA) to include "the formulation of the product." Section (V)(A)(3) of FDA's MRTPA Draft Guidance (2012) provides additional clarifications on this topic and recommends that applicants include "[d]ata establishing the stability of the product through the stated shelf life". This study establishes stability of the candidate product at ambient conditions (b) (4) following manufacturing. (b) (4)

The candidate product is a grandfathered product (FDA Grandfather Status # GF1200194) (Appendix 2.3-1), commercially marketed in the U.S. as of February 15, 2007. As such, it is not a new tobacco product as defined by FDCA Section 910(a)(1) and does not require premarket review and authorization.[1]

7.2.2. Scientific Literature Supporting Methodological Relevance

Without specific guidance from FDA on stability testing of smokeless tobacco products, ALCS designed stability studies for the candidate product using the principles of ICH Guideline Q1A(R2), which the FDA issued as *Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products* (2003) (Appendix 7.2-1)

ALCS tested five production lots of the candidate product in accordance with Appendix 7.2-1, Section 2.2.3 of the Q1A(R2) Guidance - "Selection of Batches". The candidate product was stored in the same container closure system as intended for marketing and as recommended in Appendix 7.2-1, Section 2.2.4 of the Q1A(R2) Guidance. ALCS uses fully validated analytical procedures, as recommended in Appendix 7.2-1, Section 2.2.5 of the Q1A(R2) Guidance, to measure nitrite, nitrate, oven volatiles, tobacco-specific nitrosamines, pH and water activity (Table 7.2-2 for list of constituents).

We include data on physical and chemical attributes of the candidate product such as pH, water activity, moisture content (oven volatiles), tobacco-specific nitrosamines, nitrate and nitrite of the candidate products.[2]

Methods are validated according to the ALCS Analytical Sciences Method Validation Guideline, which follows the International Conference on Harmonization (ICH) Harmonized Tripartite Guideline, Validation of Analytical Procedures: Methodology Q2B, November 1996, in addition to the U.S. Department of Health and Human Services Food and Drug Administration Guidance for Industry, Bioanalytical Method Validation, Draft Guidance,

[1] Copenhagen® Fine Cut and variants thereof have been on the market since 1822. Since 2007, USSTC made minor modifications to Copenhagen® Snuff Fine Cut, which are the subject of a separate pending Substantial Equivalence review. The candidate product subject to the MRTPA is the product for which FDA granted grandfathered status (Grandfather Number – GF1200194) on November 1, 2012.

[2] (b) (4)

Revision 1, (2013). All ALCS analytical methods used for stability testing are accredited to the ISO 17025:2005 standard by A2LA (Appendix 7.1-8, Appendix 7.1-9, and Appendix 7.1-10) with the exception of SOP 096-3841, "pH Analysis of Tobacco Lancaster" (Appendix 7.2-2) and SOP 095-5014, "Determination of Nitrite and Nitrate in Smokeless Tobacco Products by Ion Chromatography" (Appendix 7.2-3).

ALCS employs the same pH method in this study that is used to (b) (4) by USSTC factory Quality Assurance. (b) (4) . SOP 095-5014 (Appendix 7.2-3) is submitted to A2LA for addition to the laboratory's scope of accreditation and is pending at this time.

7.2.3. Experimental Design

Stability studies are conducted to assess the chemical changes to the candidate product over a (b) (4) post manufacturing. Samples are stored in commercial packaging in one environmental condition intended for ambient storage:

(b) (4)

After the candidate product is finished and packed out at the factory, the candidate product is conditioned for (b) (4) and delivered to the laboratory as defined in Table 7.2-1.

Table 7.2-1: Sample Handling Summary

Condition Designation	Storage Condition	Duration
(b) (4)		

Samples are stored at room temperature upon receipt to the laboratory and placed into an ambient controlled environment at the first study time point. Samples are pulled for testing from the ambient storage condition at (b) (4)

The five production lots of the candidate product were produced at the USSTC manufacturing facilities located in Franklin Park, Illinois (Lots 01000, 01001) and Nashville, Tennessee (Lots 01004, 01005, 01006).

7.2.4. Study Methodology

Samples are pulled for analysis from storage conditions according to the defined schedule. Three replicates of each test are conducted on five production lots. Testing three replicates is generally sufficient for most tobacco constituents, as additional replicates typically produce little improvement in the quality of data (Appendix 7.2-4). Table 7.2-2 lists the constituents measured by test in this study.

Table 7.2-2: Constituents by Test

Appendix Number	SOP Number	Common Name (CAS #, if applicable)
7.2-2	096-3841	**pH**
7.2-5	095-3330	**Oven Volatiles**
7.2-6	095-5519	**NNN** (16543-55-8), **NNK** (64091-91-4)
7.2-3	095-5014	**Nitrite** (14797-65-0)**, Nitrate** (14797-55-8)
7.2-7	095-3021	**Water Activity**

Table 7.2-3 lists the stability measurements performed at each time point in this study.

Table 7.2-3: Summary of Stability Study Sampling and Testing Schedule

Appendix Number	Time points post-manufacturing SOP# (constituents)	(b) (4)		
7.2-2	096-3841 (pH)	Y	Y	Y
7.2-5	095-3330 (oven volatiles)	Y	Y	Y
7.2-6	095-5519 (NNN, NNK)	Y	Y	Y
7.2-3	095-5014 (NO_2, NO_3)	Y	Y	Y
7.2-7	095-3021 (water activity)	Y	Y	Y

Table 7.2-4 lists the methods used for stability testing.

Table 7.2-4: Test Methods

Appendix Number	SOP Number	ALCS Methods
7.2-2	096-3841	pH Analysis of Tobacco - Lancaster
7.2-5	095-3330	Determination of Oven Volatiles, Precision Oven

Table 7.2-4: Test Methods (Continued)

Appendix Number	SOP Number	ALCS Methods
7.2-6	095-5519	Determination of TSNAs in Tobacco and Tobacco Products by LC-MS/MS
7.2-3	095-5014	Determination of Nitrite and Nitrate in Smokeless Tobacco Products by Ion Chromatography
7.2-7	095-3021	Measurement of Water Activity in Tobacco and Tobacco Products

The ALCS methods in Table 7.2-4 are described below:

Appendix 7.2-2, SOP 096-3841 pH Analysis of Tobacco - Lancaster

Approximately 5.0 g of material is extracted with 100 mL of deionized water. The sample mixture is extracted by stirring for approximately sixty (60) minutes. The pH of the aqueous extract is then measured.

Appendix 7.2-5, SOP 095-3330 Determination of Oven Volatiles, Precision Oven

Approximately 5.0 g of material is weighed into a dried and tared aluminum dish. Using a forced-air oven heated to 100 °C, the sample is heated for approximately three hours. The sample is covered, cooled to room temperature in a desiccator, and then weighed. The percent oven volatiles (OV) is calculated by dividing the weight loss by the original sample weight and multiplying the result by 100.

Appendix 7.2-6, SOP 095-5519 Determination of TSNAs in Tobacco and Tobacco Products by LC-MS/MS

Deuterated internal standards are added to approximately 0.75 g of tobacco. This is followed by extraction with ammonium acetate, rotating and cleaning the sample extract by solid-phase extraction (SPE) and analyzing the sample by liquid chromatography with tandem mass spectrometry (LC/MS/MS).

Appendix 7.2-3, SOP 095-5014 Determination of Nitrite and Nitrate in Smokeless Tobacco Products by Ion Chromatography

Approximately 2.0 g of tobacco is extracted using 100 mL of deionized water with agitation by a platform shaker for 30 minutes. The sample extract is then analyzed by liquid (anion exchange) chromatography using an external standard calibration.

Appendix 7.2-7, SOP 095-3021 Measurement of Water Activity in Tobacco and Tobacco Products

Water activity is measured using a Decagon Aqualab water activity meter equipped with tunable diode laser (TDL) detection. Tobacco sample is transferred into a 4 cm diameter sample cup so as to fill the bottom surface of the sample cup.

7.2.5. Study Limitations

SOP 096-3841, “Determination of pH in Smokeless Tobacco Products – Lancaster,” (Appendix 7.2-2) is an ALCS validated method, but not accredited under the ALCS scope of

accreditation to the ISO 17025 standard. However, this work is performed under the same quality system that is used for ISO 17025 reporting. SOP 095-5014, "Determination of Nitrite and Nitrate in Smokeless Tobacco Products by Ion Chromatography," (Appendix 7.2-3) is an ALCS validated method and is submitted for addition to the laboratory's scope of accreditation to the ISO 17025 standard.

7.2.6. Results

The study report summarizes the product data in tabular form with select measures also reported in graphical form. Data Table 7.2-5 through Table 7.2-19 provide stability data on an as-is basis including the mean value and 95% confidence interval for each lot for each time point. Data Table 7.2-20 through Table 7.2-22 provides stability data on an as-is basis for the overall mean and 95% confidence interval for all five lots for each time point. Data Table 7.2-23 through Table 7.2-27 provides stability data on an as-is basis for individual constituent data shown as replicates and mean with 95% confidence intervals for each lot. We further represent the results as plots of summary of select end-points for five (5) lots in Figure 7.2-1 through Figure 7.2-7.

7.2.7. Conclusion

We provide evidence that the constituents in the candidate product are stable over a (b) (4) (b) (4) from the date of manufacture. We do not observe any trends of increases in NNN, NNK, nitrate, nitrite and water activity levels over a (b) (4) from the date of manufacture. (b) (4)

Table 7.2-5: Summary of Lot Results (As-Is) – Lot # 01000 ((b) (4)); Mfg Date: March 8, 2017

Constituent (Common Name)	CAS #	Units	Mean Value	95% CI	Sample Size	Test Date	Measurement Method
N-nitrosonornicotine (NNN)	16543-55-8	ng/g	1613	41.0	3	03/24/17	095-5519
4-(N-methyl-N-nitrosoamino)-1-(3-pyridyl)-1-butanone (NNK)	64091-91-4	ng/g	547	15.8	3	03/24/17	095-5519
Nitrite	14797-65-0	µg/g	12.2	1.05	3	03/24/17	095-5014
Nitrate	14797-55-8	µg/g	12564	451	3	03/24/17	095-5014
pH	N/A	N/A	7.82	0.0620	3	03/24/17	096-3841
Oven Volatiles (OV)	N/A	%	54.2	0.0509	3	03/24/17	095-3330
Water Activity (A_W)	N/A	N/A	0.843	0.00176	3	03/24/17	095-3021

N/A = Not Applicable

Table 7.2-6: Summary of Lot Results (As-Is) – Lot # 01000 ((b) (4) ; Mfg Date: March 8, 2017

Constituent (Common Name)	CAS #	Units	Mean Value	95% CI	Sample Size	Test Date	Measurement Method
N-nitrosonornicotine (NNN)	16543-55-8	ng/g	1682	80.5	3	04/10/17	095-5519
4-(N-methyl-N-nitrosoamino)-1-(3-pyridyl)-1-butanone (NNK)	64091-91-4	ng/g	530	21.7	3	04/10/17	095-5519
Nitrite	14797-65-0	µg/g	11.2	0.194	3	04/10/17	095-5014
Nitrate	14797-55-8	µg/g	12260	307	3	04/10/17	095-5014
pH	N/A	N/A	7.72	0.00379	3	04/10/17	096-3841
Oven Volatiles (OV)	N/A	%	53.5	0.136	3	04/10/17	095-3330
Water Activity (A_W)	N/A	N/A	0.841	0.000941	3	04/10/17	095-3021

N/A = Not Applicable

Table 7.2-7: Summary of Lot Results (As-Is) – Lot # 01000 (b) (4)); Mfg Date: March 8, 2017

Constituent (Common Name)	CAS #	Units	Mean Value	95% CI	Sample Size	Test Date	Measurement Method
N-nitrosonornicotine (NNN)	16543-55-8	ng/g	1664	19.2	3	04/20/17	095-5519
4-(N-methyl-N-nitrosoamino)-1-(3-pyridyl)-1-butanone (NNK)	64091-91-4	ng/g	551	6.00	3	04/20/17	095-5519
Nitrite	14797-65-0	µg/g	10.4	0.236	3	04/20/17	095-5014
Nitrate	14797-55-8	µg/g	12682	351	3	04/20/17	095-5014
pH	N/A	N/A	7.67	0.0155	3	04/20/17	096-3841
Oven Volatiles (OV)	N/A	%	53.1	0.136	3	04/20/17	095-3330
Water Activity (A_W)	N/A	N/A	0.842	0.00883	3	04/20/17	095-3021

N/A = Not Applicable

Table 7.2-8: Summary of Lot Results (As-Is) – Lot # 01001 (b) (4); Mfg Date: March 8, 2017

Constituent (Common Name)	CAS #	Units	Mean Value	95% CI	Sample Size	Test Date	Measurement Method
N-nitrosonornicotine (NNN)	16543-55-8	ng/g	N/T	N/T	0	N/A	095-5519
4-(N-methyl-N-nitrosoamino)-1-(3-pyridyl)-1-butanone (NNK)	64091-91-4	ng/g	N/T	N/T	0	N/A	095-5519
Nitrite	14797-65-0	µg/g	N/T	N/T	0	N/A	095-5014
Nitrate	14797-55-8	µg/g	N/T	N/T	0	N/A	095-5014
pH	N/A	N/A	N/T	N/T	0	N/A	096-3841
Oven Volatiles (OV)	N/A	%	N/T	N/T	0	N/A	095-3330
Water Activity (A_W)	N/A	N/A	N/T	N/T	0	N/A	095-3021

N/A = Not Applicable; N/T = Not Tested

(b) (4)

Table 7.2-9: Summary of Lot Results (As-Is) – Lot # 01001 (b) (4); Mfg Date: March 8, 2017

Constituent (Common Name)	CAS #	Units	Mean Value	95% CI	Sample Size	Test Date	Measurement Method
N-nitrosonornicotine (NNN)	16543-55-8	ng/g	1667	105	3	04/06/17	095-5519
4-(N-methyl-N-nitrosoamino)-1-(3-pyridyl)-1-butanone (NNK)	64091-91-4	ng/g	545	29.5	3	04/06/17	095-5519
Nitrite	14797-65-0	µg/g	9.90	0.424	3	04/06/17	095-5014
Nitrate	14797-55-8	µg/g	12660	309	3	04/06/17	095-5014
pH	N/A	N/A	7.79	0.0179	3	04/06/17	096-3841
Oven Volatiles (OV)	N/A	%	54.0	0.0455	3	04/06/17	095-3330
Water Activity (A_W)	N/A	N/A	0.840	0.000517	3	04/06/17	095-3021

N/A = Not Applicable

Table 7.2-10: Summary of Lot Results (As-Is) – Lot # 01001 (b) (4); Mfg Date: March 8, 2017

Constituent (Common Name)	CAS #	Units	Mean Value	95% CI	Sample Size	Test Date	Measurement Method
N-nitrosonornicotine (NNN)	16543-55-8	ng/g	1689	88.1	3	04/20/17	095-5519
4-(N-methyl-N-nitrosoamino)-1-(3-pyridyl)-1-butanone (NNK)	64091-91-4	ng/g	568	34.7	3	04/20/17	095-5519
Nitrite	14797-65-0	µg/g	9.09	0.558	3	04/20/17	095-5014
Nitrate	14797-55-8	µg/g	12714	444	3	04/20/17	095-5014
pH	N/A	N/A	7.76	0.00872	3	04/20/17	096-3841
Oven Volatiles (OV)	N/A	%	53.6	0.189	3	04/20/17	095-3330
Water Activity (A_W)	N/A	N/A	0.841	0.00137	3	04/20/17	095-3021

N/A = Not Applicable

Table 7.2-11: Summary of Lot Results (As-Is) – Lot # 01004 (b) (4) Mfg Date: June 2, 2017

Constituent (Common Name)	CAS #	Units	Mean Value	95% CI	Sample Size	Test Date	Measurement Method
N-nitrosonornicotine (NNN)	16543-55-8	ng/g	1827	11.8	3	06/19/17	095-5519
4-(N-methyl-N-nitrosoamino)-1-(3-pyridyl)-1-butanone (NNK)	64091-91-4	ng/g	410	4.53	3	06/19/17	095-5519
Nitrite	14797-65-0	µg/g	ND	N/A	3	06/19/17	095-5014
Nitrate	14797-55-8	µg/g	12098	680	3	06/19/17	095-5014
pH	N/A	N/A	7.76	0.0567	3	06/19/17	096-3841
Oven Volatiles (OV)	N/A	%	54.7	0.319	3	06/19/17	095-3330
Water Activity (A_W)	N/A	N/A	0.847	0.00143	3	06/19/17	095-3021

N/A = Not Applicable; ND = Not Detected

Table 7.2-12: Summary of Lot Results (As-Is) – Lot # 01004 (b) (4)
Mfg Date: June 2, 2017

Constituent (Common Name)	CAS #	Units	Mean Value	95% CI	Sample Size	Test Date	Measurement Method
N-nitrosonornicotine (NNN)	16543-55-8	ng/g	1853	125	3	07/05/17	095-5519
4-(N-methyl-N-nitrosoamino)-1-(3-pyridyl)-1-butanone (NNK)	64091-91-4	ng/g	423	16.7	3	07/05/17	095-5519
Nitrite	14797-65-0	µg/g	ND	N/A	3	07/05/17	095-5014
Nitrate	14797-55-8	µg/g	12426	368	3	07/05/17	095-5014
pH	N/A	N/A	7.68	0.0583	3	07/05/17	096-3841
Oven Volatiles (OV)	N/A	%	54.2	0.412	3	07/05/17	095-3330
Water Activity (A_W)	N/A	N/A	0.848	0.00473	3	07/05/17	095-3021

N/A = Not Applicable; ND = Not Detected

Table 7.2-13: Summary of Lot Results (As-Is) – Lot # 01004 (b) (4)
Mfg Date: June 2, 2017

Constituent (Common Name)	CAS #	Units	Mean Value	95% CI	Sample Size	Test Date	Measurement Method
N-nitrosonornicotine (NNN)	16543-55-8	ng/g	1782	39.4	3	07/19/17	095-5519
4-(N-methyl-N-nitrosoamino)-1-(3-pyridyl)-1-butanone (NNK)	64091-91-4	ng/g	394	15.7	3	07/19/17	095-5519
Nitrite	14797-65-0	µg/g	ND	N/A	3	07/19/17	095-5014
Nitrate	14797-55-8	µg/g	12257	163	3	07/19/17	095-5014
pH	N/A	N/A	7.62	0.119	3	07/19/17	096-3841
Oven Volatiles (OV)	N/A	%	54.2	0.201	3	07/19/17	095-3330
Water Activity (A_W)	N/A	N/A	0.843	0.00141	3	07/19/17	095-3021

N/A = Not Applicable; ND = Not Detected

Table 7.2-14: Summary of Lot Results (As-Is) – Lot # 01005 (b) (4) ; Mfg Date: June 2, 2017

Constituent (Common Name)	CAS #	Units	Mean Value	95% CI	Sample Size	Test Date	Measurement Method
N-nitrosonornicotine (NNN)	16543-55-8	ng/g	1823	68.4	3	06/19/17	095-5519
4-(N-methyl-N-nitrosoamino)-1-(3-pyridyl)-1-butanone (NNK)	64091-91-4	ng/g	420	29.9	3	06/19/17	095-5519
Nitrite	14797-65-0	µg/g	ND	N/A	3	06/19/17	095-5014
Nitrate	14797-55-8	µg/g	11752	401	3	06/19/17	095-5014
pH	N/A	N/A	7.80	0.00143	3	06/19/17	096-3841
Oven Volatiles (OV)	N/A	%	54.7	0.0764	3	06/19/17	095-3330
Water Activity (A_W)	N/A	N/A	0.848	0.000625	3	06/19/17	095-3021

N/A = Not Applicable; ND = Not Detected

Table 7.2-15: Summary of Lot Results (As-Is) – Lot # 01005 (b) (4) Mfg Date: June 2, 2017

Constituent (Common Name)	CAS #	Units	Mean Value	95% CI	Sample Size	Test Date	Measurement Method
N-nitrosonornicotine (NNN)	16543-55-8	ng/g	1867	65.8	3	07/05/17	095-5519
4-(N-methyl-N-nitrosoamino)-1-(3-pyridyl)-1-butanone (NNK)	64091-91-4	ng/g	438	17.1	3	07/05/17	095-5519
Nitrite	14797-65-0	µg/g	ND	N/A	3	07/05/17	095-5014
Nitrate	14797-55-8	µg/g	12497	509	3	07/05/17	095-5014
pH	N/A	N/A	7.72	0.00799	3	07/05/17	096-3841
Oven Volatiles (OV)	N/A	%	54.5	0.100	3	07/05/17	095-3330
Water Activity (A_W)	N/A	N/A	0.845	0.00197	3	07/05/17	095-3021

N/A = Not Applicable; ND = Not Detected

Table 7.2-16: Summary of Lot Results (As-Is) – Lot # 01005 (b) (4)
Mfg Date: June 2, 2017

Constituent (Common Name)	CAS #	Units	Mean Value	95% CI	Sample Size	Test Date	Measurement Method
N-nitrosonornicotine (NNN)	16543-55-8	ng/g	1819	60.4	3	07/19/17	095-5519
4-(N-methyl-N-nitrosoamino)-1-(3-pyridyl)-1-butanone (NNK)	64091-91-4	ng/g	406	20.3	3	07/19/17	095-5519
Nitrite	14797-65-0	µg/g	ND	N/A	3	07/19/17	095-5014
Nitrate	14797-55-8	µg/g	12145	256	3	07/19/17	095-5014
pH	N/A	N/A	7.62	0.0564	3	07/19/17	096-3841
Oven Volatiles (OV)	N/A	%	53.9	0.222	3	07/19/17	095-3330
Water Activity (A_W)	N/A	N/A	0.841	0.000517	3	07/19/17	095-3021

N/A = Not Applicable; ND = Not Detected

Table 7.2-17: Summary of Lot Results (As-Is) – Lot # 01006 (b) (4)
Mfg Date: June 2, 2017

Constituent (Common Name)	CAS #	Units	Mean Value	95% CI	Sample Size	Test Date	Measurement Method
N-nitrosonornicotine (NNN)	16543-55-8	ng/g	1849	41.2	3	06/19/17	095-5519
4-(N-methyl-N-nitrosoamino)-1-(3-pyridyl)-1-butanone (NNK)	64091-91-4	ng/g	434	23.1	3	06/19/17	095-5519
Nitrite	14797-65-0	µg/g	ND	N/A	3	06/19/17	095-5014
Nitrate	14797-55-8	µg/g	11949	603	3	06/19/17	095-5014
pH	N/A	N/A	7.78	0.00717	3	06/19/17	096-3841
Oven Volatiles (OV)	N/A	%	54.5	0.00617	3	06/19/17	095-3330
Water Activity (A_W)	N/A	N/A	0.846	0.00152	3	06/19/17	095-3021

N/A = Not Applicable; ND = Not Detected

Table 7.2-18: Summary of Lot Results (As-Is) – Lot # 01006 (b) (4) ; Mfg Date: June 2, 2017

Constituent (Common Name)	CAS #	Units	Mean Value	95% CI	Sample Size	Test Date	Measurement Method
N-nitrosonornicotine (NNN)	16543-55-8	ng/g	1815	40.2	3	07/05/17	095-5519
4-(N-methyl-N-nitrosoamino)-1-(3-pyridyl)-1-butanone (NNK)	64091-91-4	ng/g	441	15.3	3	07/05/17	095-5519
Nitrite	14797-65-0	µg/g	ND	N/A	3	07/05/17	095-5014
Nitrate	14797-55-8	µg/g	12264	354	3	07/05/17	095-5014
pH	N/A	N/A	7.72	0.0174	3	07/05/17	096-3841
Oven Volatiles (OV)	N/A	%	54.3	0.353	3	07/05/17	095-3330
Water Activity (A_W)	N/A	N/A	0.844	0.000799	3	07/05/17	095-3021

N/A = Not Applicable; ND = Not Detected

Table 7.2-19: Summary of Lot Results (As-Is) – Lot # 01006 (b) (4) Mfg Date: June 2, 2017

Constituent (Common Name)	CAS #	Units	Mean Value	95% CI	Sample Size	Test Date	Measurement Method
N-nitrosonornicotine (NNN)	16543-55-8	ng/g	1821	44.2	3	07/19/17	095-5519
4-(N-methyl-N-nitrosoamino)-1-(3-pyridyl)-1-butanone (NNK)	64091-91-4	ng/g	407	7.37	3	07/19/17	095-5519
Nitrite	14797-65-0	µg/g	ND	N/A	3	07/19/17	095-5014
Nitrate	14797-55-8	µg/g	11985	166	3	07/19/17	095-5014
pH	N/A	N/A	7.64	0.0345	3	07/19/17	096-3841
Oven Volatiles (OV)	N/A	%	54.2	0.268	3	07/19/17	095-3330
Water Activity (A_W)	N/A	N/A	0.848	0.00108	3	07/19/17	095-3021

N/A = Not Applicable; ND = Not Detected

Table 7.2-20: Summary of Results (As-Is) – Lots 01000, 01004, 01005, 01006 (b) (4)

Constituent (Common Name)	CAS #	Units	Mean Value	95% CI	Sample Size	Measurement Method
N-nitrosonornicotine (NNN)	16543-55-8	ng/g	1778	176.4	4	095-5519
4-(N-methyl-N-nitrosoamino)-1-(3-pyridyl)-1-butanone (NNK)	64091-91-4	ng/g	453	101.5	4	095-5519
Nitrite	14797-65-0	µg/g	2.64	8.50	4	095-5014
Nitrate	14797-55-8	µg/g	12091	551	4	095-5014
pH	N/A	N/A	7.79	0.0393	4	096-3841
Oven Volatiles (OV)	N/A	%	54.5	0.391	4	095-3330
Water Activity (A_W)	N/A	N/A	0.846	0.00321	4	095-3021

N/A = Not Applicable
NOTE (b) (4)

Table 7.2-21: Summary of Results (As-Is) – Lots 01000, 01001, 01004, 01005, 01006 ((b) (4)

Constituent (Common Name)	CAS #	Units	Mean Value	95% CI	Sample Size	Measurement Method
N-nitrosonornicotine (NNN)	16543-55-8	ng/g	1777	118	5	095-5519
4-(N-methyl-N-nitrosoamino)-1-(3-pyridyl)-1-butanone (NNK)	64091-91-4	ng/g	475	71.1	5	095-5519
Nitrite	14797-65-0	µg/g	3.68	6.61	5	095-5014
Nitrate	14797-55-8	µg/g	12422	209	5	095-5014
pH	N/A	N/A	7.73	0.0475	5	096-3841
Oven Volatiles (OV)	N/A	%	54.1	0.456	5	095-3330
Water Activity (A_W)	N/A	N/A	0.844	0.00378	5	095-3021

N/A = Not Applicable

Table 7.2-22: Summary of Results (As-Is) – Lots 01000, 01001, 01004, 01005, 01006 (b) (4)

Constituent (Common Name)	CAS #	Units	Mean Value	95% CI	Sample Size	Measurement Method
N-nitrosonornicotine (NNN)	16543-55-8	ng/g	1755	91.7	5	095-5519
4-(N-methyl-N-nitrosoamino)-1-(3-pyridyl)-1-butanone (NNK)	64091-91-4	ng/g	465	107	5	095-5519
Nitrite	14797-65-0	µg/g	3.41	6.11	5	095-5014
Nitrate	14797-55-8	µg/g	12357	405	5	095-5014
pH	N/A	N/A	7.66	0.0727	5	096-3841
Oven Volatiles (OV)	N/A	%	53.8	0.574	5	095-3330
Water Activity (A_W)	N/A	N/A	0.843	0.00329	5	095-3021

N/A = Not Applicable

Table 7.2-23: Individual Lot Results (As-Is) – Lot # 01000; Mfg Date: March 8, 2017

Constituent (Common Name)	CAS #	Units	Replicate	Values (b) (4)		
			Test Date:	**3/24/2017**	**4/10/2017**	**4/20/2017**
N-nitrosonornicotine (NNN)	16543-55-8	ng/g	1	1615	1677	1667
			2	1628	1653	1655
			3	1595	1717	1669
			Mean	**1613**	**1682**	**1664**
			95% CI	**41.0**	**80.5**	**19.2**
4-(N-methyl-N-nitrosoamino)-1-(3-pyridyl)-1-butanone (NNK)	64091-91-4	ng/g	1	553	532	551
			2	548	537	553
			3	541	520	548
			Mean	**547**	**530**	**551**
			95% CI	**15.8**	**21.7**	**6.00**
Nitrite	14797-65-0	µg/g	1	12.7	11.1	10.5
			2	11.8	11.2	10.3
			3	12.1	11.3	10.4
			Mean	**12.2**	**11.2**	**10.4**
			95% CI	**1.05**	**0.194**	**0.236**
Nitrate	14797-55-8	µg/g	1	12435	12122	12560

Constituent (Common Name)	CAS #	Units	Replicate	Values		
				(b) (4)		
			2	12487	12298	12836
			3	12772	12360	12649
			Mean	**12564**	**12260**	**12682**
			95% CI	**451**	**307**	**351**
pH	N/A	N/A	1	7.83	7.72	7.66
			2	7.84	7.72	7.67
			3	7.79	7.73	7.67
			Mean	**7.82**	**7.72**	**7.67**
			95% CI	**0.0620**	**0.00379**	**0.0155**
Oven Volatiles	N/A	%	1	54.1	53.5	53.1
			2	54.2	53.5	53.1
			3	54.2	53.6	53.2
			Mean	**54.2**	**53.5**	**53.1**
			95% CI	**0.0509**	**0.136**	**0.136**
			2	0.844	0.841	0.846
			3	0.842	0.841	0.838
			Mean	**0.843**	**0.841**	**0.842**
			95% CI	**0.00176**	**0.000941**	**0.00883**
Water Activity	N/A	N/A	1	0.843	0.842	0.842

N/A = Not Applicable; ND = Not Detected

Table 7.2-24: Individual Lot Results (As-Is) – Lot # 01001; Mfg Date: March 8, 2017

Constituent (Common Name)	CAS #	Units	Replicate	Values		
				(b) (4)		
			Test Date:	**3/24/2017**	**4/6/2017**	**4/20/2017**
N-nitrosonornicotine (NNN)	16543-55-8	ng/g	1	-----	1705	1678
			2	-----	1622	1661
			3	-----	1674	1729
			Mean	-----	**1667**	**1689**
			95% CI	-----	**105**	**88.1**
4-(N-methyl-N-nitrosoamino)-1-(3-pyridyl)-1-butanone (NNK)	64091-91-4	ng/g	1	-----	531	579

Constituent (Common Name)	CAS #	Units	Replicate	Values		
						(b) (4)
			2	-----	550	572
			3	-----	554	552
			Mean	-----	**545**	**568**
			95% CI	-----	**29.5**	**34.7**
Nitrite	14797-65-0	µg/g	1	-----	10.1	8.95
			2	-----	9.94	8.98
			3	-----	9.72	9.35
			Mean	-----	**9.90**	**9.09**
			95% CI	-----	**0.424**	**0.558**
Nitrate	14797-55-8	µg/g	1	-----	12781	12529
			2	-----	12668	12729
			3	-----	12532	12886
			Mean	-----	**12660**	**12714**
			95% CI	-----	**309**	**444**
pH	N/A	N/A	1	-----	7.78	7.76
			2	-----	7.79	7.76
			3	-----	7.79	7.76
			Mean	-----	**7.79**	**7.76**
			95% CI	-----	**0.0179**	**0.00872**
Oven Volatiles	N/A	%	1	-----	54.0	53.5
			2	-----	54.0	53.7
			3	-----	54.0	53.6
			Mean	-----	**54.0**	**53.6**
			95% CI	-----	**0.0455**	**0.189**
Water Activity	N/A	N/A	1	-----	0.840	0.841
			2	-----	0.840	0.842
			3	-----	0.840	0.841
			Mean	-----	**0.840**	**0.841**
			95% CI	-----	**0.000517**	**0.00137**

N/A = Not Applicable

[1] (b) (4)

Table 7.2-25: Individual Lot Results (As-Is) – Lot # 01004; Mfg Date: June 2, 2017

Constituent (Common Name)	CAS #	Units	Replicate	Values (b) (4)		
			Test Date:	**6/19/2017**	**7/5/2017**	**7/19/2017**
N-nitrosonornicotine (NNN)	16543-55-8	ng/g	1	1829	1856	1800
			2	1822	1802	1769
			3	1830	1902	1777
			Mean	**1827**	**1853**	**1782**
			95% CI	**11.8**	**125**	**39.4**
4-(N-methyl-N-nitrosoamino)-1-(3-pyridyl)-1-butanone (NNK)	64091-91-4	ng/g	1	410	415	387
			2	408	425	394
			3	412	428	400
			Mean	**410**	**423**	**394**
			95% CI	**4.53**	**16.7**	**15.7**
Nitrite	14797-65-0	µg/g	1	ND	ND	ND
			2	ND	ND	ND
			3	ND	ND	ND
			Mean	**ND**	**ND**	**ND**
			95% CI	**N/A**	**N/A**	**N/A**
Nitrate	14797-55-8	µg/g	1	12287	12457	12289
			2	11784	12265	12182
			3	12223	12556	12301
			Mean	**12098**	**12426**	**12257**
			95% CI	**680**	**368**	**163**
pH	N/A	N/A	1	7.74	7.65	7.64
			2	7.78	7.69	7.65
			3	7.77	7.70	7.56
			Mean	**7.76**	**7.68**	**7.62**
			95% CI	**0.0567**	**0.0583**	**0.119**
Oven Volatiles	N/A	%	1	54.5	54.1	54.2
			2	54.8	54.4	54.3
			3	54.6	54.1	54.2
			Mean	**54.7**	**54.2**	**54.2**
			95% CI	**0.319**	**0.412**	**0.201**
Water Activity	N/A	N/A	1	0.846	0.846	0.843

Constituent (Common Name)	CAS #	Units	Replicate	Values		
				(b) (4)		
			2	0.847	0.848	0.843
			3	0.847	0.849	0.844
			Mean	**0.847**	**0.848**	**0.843**
			95% CI	**0.00143**	**0.00473**	**0.00141**

N/A = Not Applicable; ND = Not Detected

Table 7.2-26: Individual Lot Results (As-Is) – Lot # 01005; Mfg Date: June 2, 2017

Constituent (Common Name)	CAS #	Units	Replicate	Values		
				(b) (4)		
			Test Date:	**6/19/2017**	**7/5/2017**	**7/19/2017**
N-nitrosonornicotine (NNN)	16543-55-8	ng/g	1	1795	1838	1833
			2	1850	1872	1834
			3	1824	1890	1791
			Mean	**1823**	**1867**	**1819**
			95% CI	**68.4**	**65.8**	**60.4**
4-(N-methyl-N-nitrosoamino)-1-(3-pyridyl)-1-butanone (NNK)	64091-91-4	ng/g	1	431	441	403
			2	420	431	416
			3	407	444	400
			Mean	**420**	**438**	**406**
			95% CI	**29.9**	**17.1**	**20.3**
Nitrite	14797-65-0	µg/g	1	ND	ND	ND
			2	ND	ND	ND
			3	ND	ND	ND
			Mean	**ND**	**ND**	**ND**
			95% CI	**N/A**	**N/A**	**N/A**
Nitrate	14797-55-8	µg/g	1	11924	12680	12258
			2	11728	12536	12056
			3	11603	12276	12122
			Mean	**11752**	**12497**	**12145**
			95% CI	**401**	**509**	**256**
pH	N/A	N/A	1	7.80	7.72	7.63

Constituent (Common Name)	CAS #	Units	Replicate	Values (b) (4)		
			2	7.80	7.72	7.60
			3	7.80	7.73	7.64
			Mean	**7.80**	**7.72**	**7.62**
			95% CI	**0.00143**	**0.00799**	**0.0564**
Oven Volatiles	N/A	%	1	54.7	54.4	53.9
			2	54.7	54.5	53.8
			3	54.7	54.5	54.0
			Mean	**54.7**	**54.5**	**53.9**
			95% CI	**0.0764**	**0.100**	**0.222**
Water Activity	N/A	N/A	1	0.848	0.844	0.841
			2	0.848	0.845	0.842
			3	0.848	0.846	0.841
			Mean	**0.848**	**0.845**	**0.841**
			95% CI	**0.000625**	**0.00197**	**0.000517**

N/A = Not Applicable; ND = Not Detected

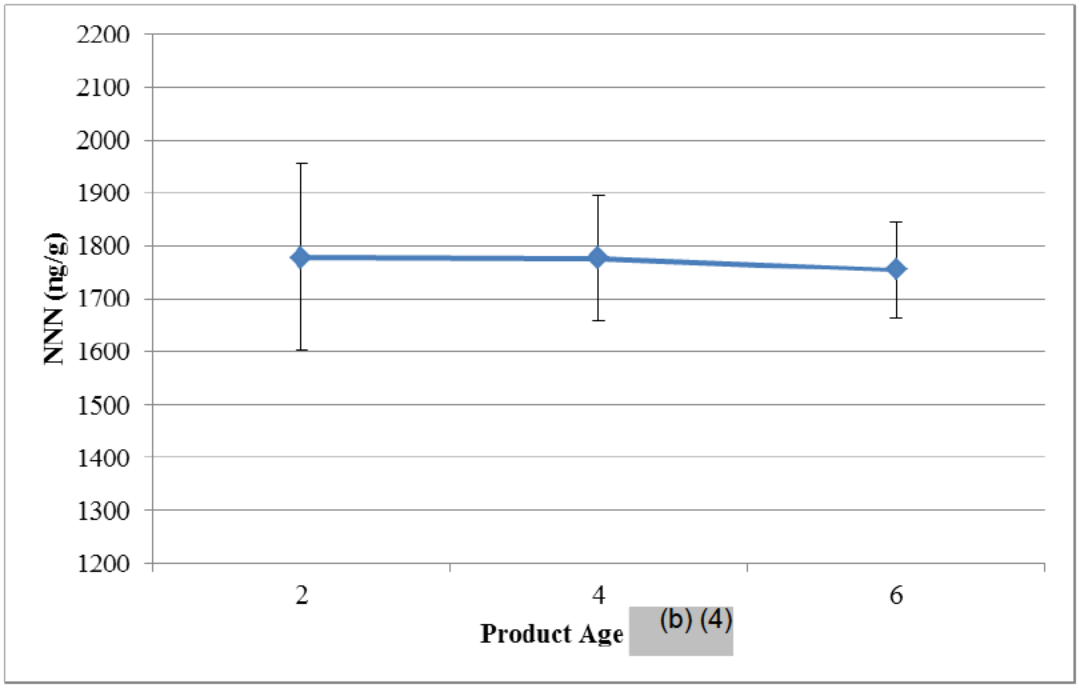
Table 7.2-27: Individual Lot Results (As-Is) – Lot # 01006; Mfg Date: June 2, 2017

Constituent (Common Name)	CAS #	Units	Replicate	Values (b) (4)		
			Test Date:	**6/19/2017**	**7/5/2017**	**7/19/2017**
N-nitrosonornicotine (NNN)	16543-55-8	ng/g	1	1863	1815	1814
			2	1831	1799	1807
			3	1855	1831	1841
			Mean	**1849**	**1815**	**1821**
			95% CI	**41.2**	**40.2**	**44.2**
4-(N-methyl-N-nitrosoamino)-1-(3-pyridyl)-1-butanone (NNK)	64091-91-4	ng/g	1	430	435	407
			2	445	447	409
			3	428	441	403
			Mean	**434**	**441**	**407**
			95% CI	**23.1**	**15.3**	**7.37**
Nitrite	14797-65-0	µg/g	1	ND	ND	ND

Constituent (Common Name)	CAS #	Units	Replicate	Values		
				(b) (4)		
			2	ND	ND	ND
			3	ND	ND	ND
			Mean	**ND**	**ND**	**ND**
			95% CI	**N/A**	**N/A**	**N/A**
Nitrate	14797-55-8	µg/g	1	12155	12340	12048
			2	11681	12100	11915
			3	12011	12354	11994
			Mean	**11949**	**12264**	**11985**
			95% CI	**603**	**354**	**166**
pH	N/A	N/A	1	7.78	7.72	7.62
			2	7.78	7.72	7.64
			3	7.78	7.73	7.65
			Mean	**7.78**	**7.72**	**7.64**
			95% CI	**0.00717**	**0.0174**	**0.0345**
Oven Volatiles	N/A	%	1	54.5	54.2	54.2
			2	54.5	54.4	54.1
			3	54.5	54.4	54.3
			Mean	**54.5**	**54.3**	**54.2**
			95% CI	**0.00617**	**0.353**	**0.268**
Water Activity	N/A	N/A	1	0.846	0.844	0.848
			2	0.847	0.845	0.847
			3	0.846	0.844	0.847
			Mean	**0.846**	**0.844**	**0.848**
			95% CI	**0.00152**	**0.000799**	**0.00108**

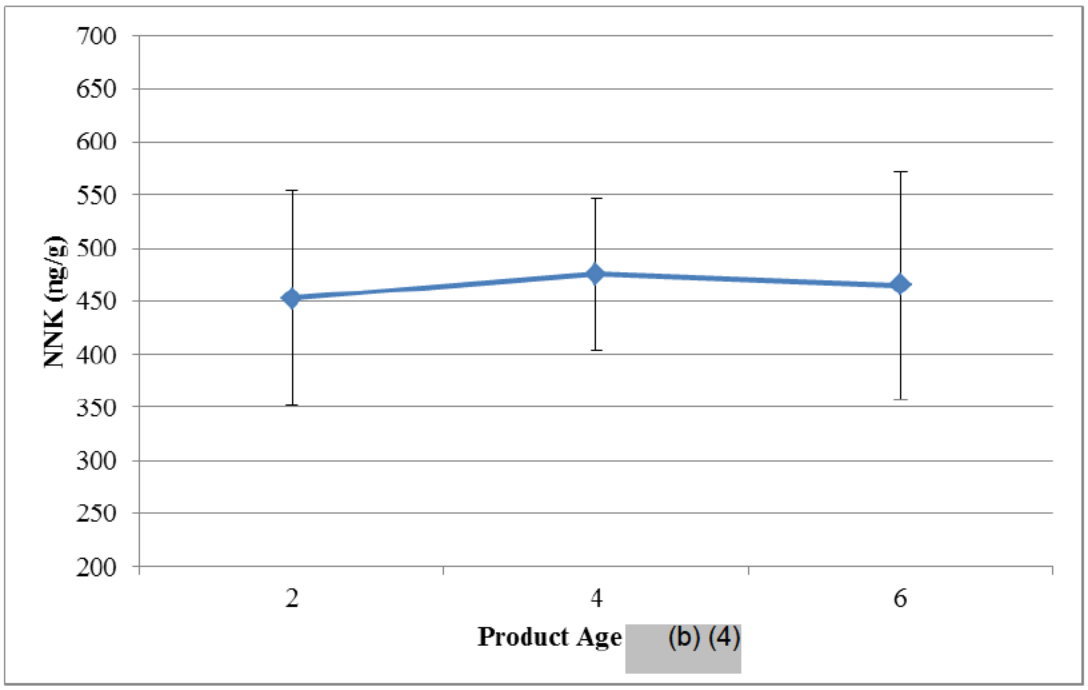
N/A = Not Applicable; ND = Not Detected

Figure 7.2-1: Candidate Product 5-Lot Summary: NNN Stability (b) (4)



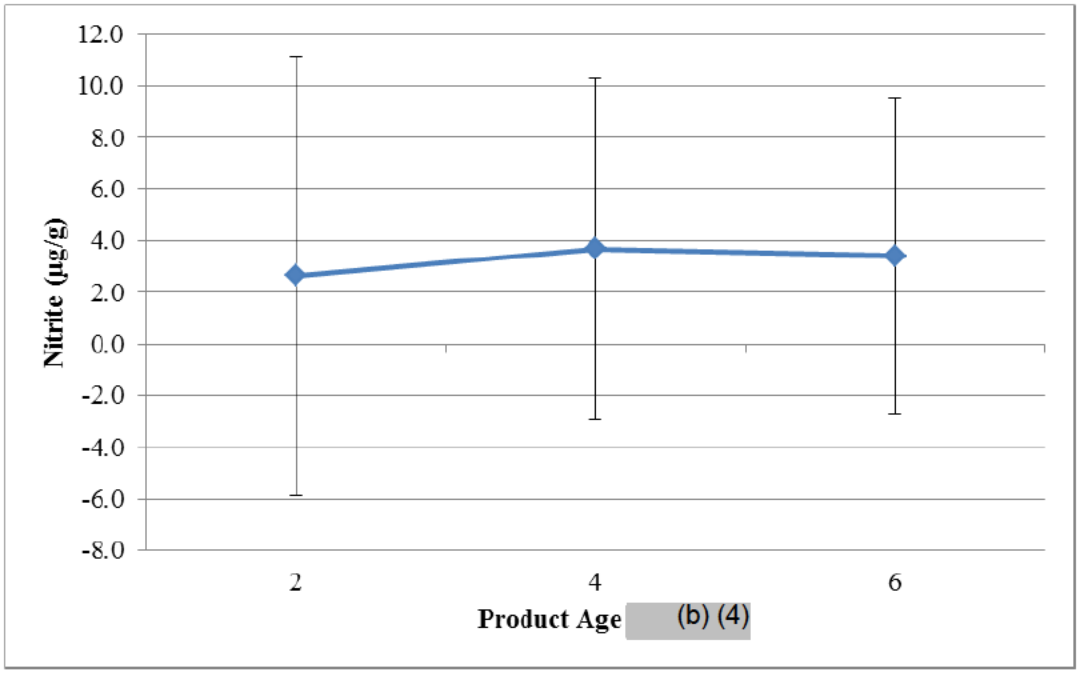
NOTE: Error bars represent the 95 % Confidence Interval.

Figure 7.2-2: Candidate Product 5-Lot Summary: NNK Stability (b) (4)



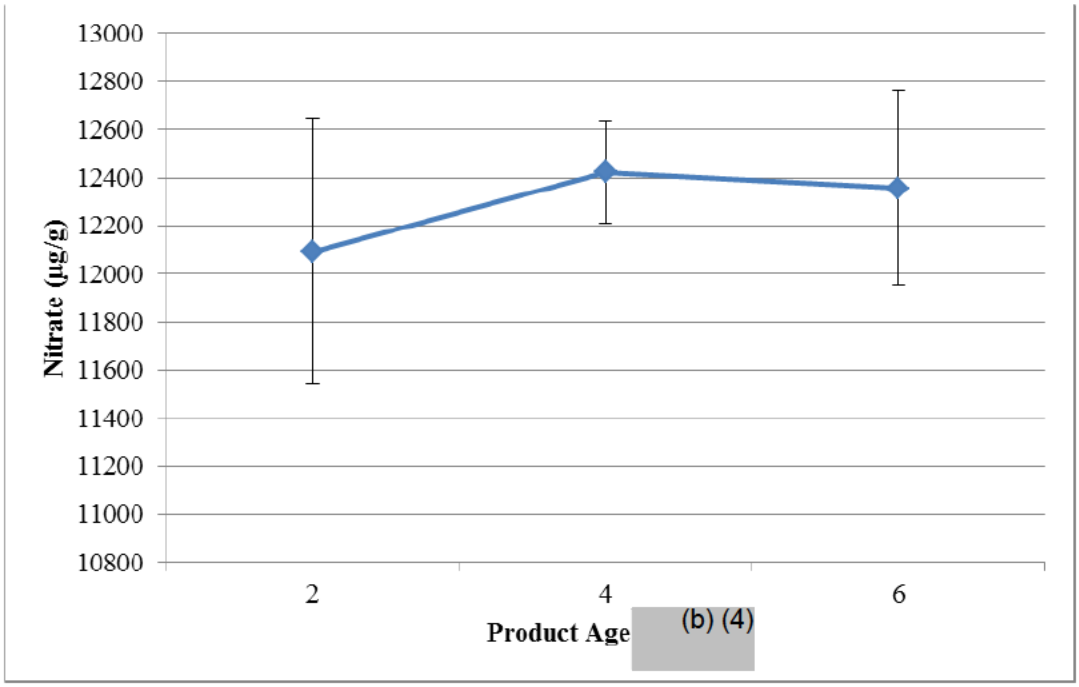
NOTE: Error bars represent the 95 % Confidence Interval.

Figure 7.2-3: Candidate Product 5-Lot Summary: Nitrite Stability (b) (4)



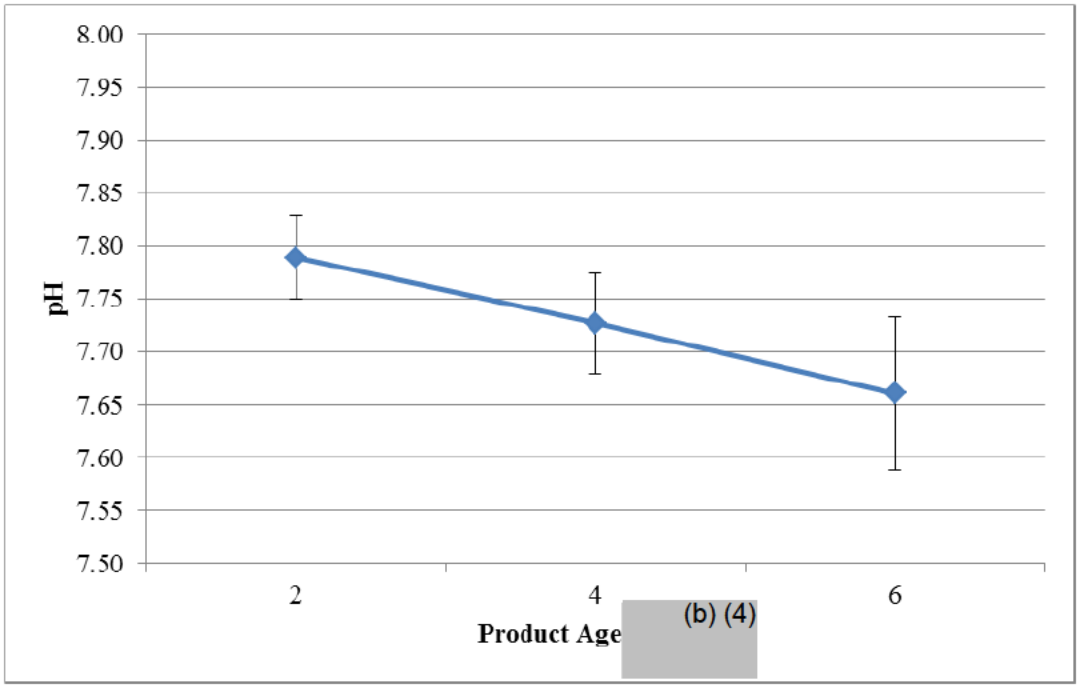
NOTE: Error bars represent the 95 % Confidence Interval.

Figure 7.2-4: Candidate Product 5-Lot Summary: Nitrate Stability (b) (4)



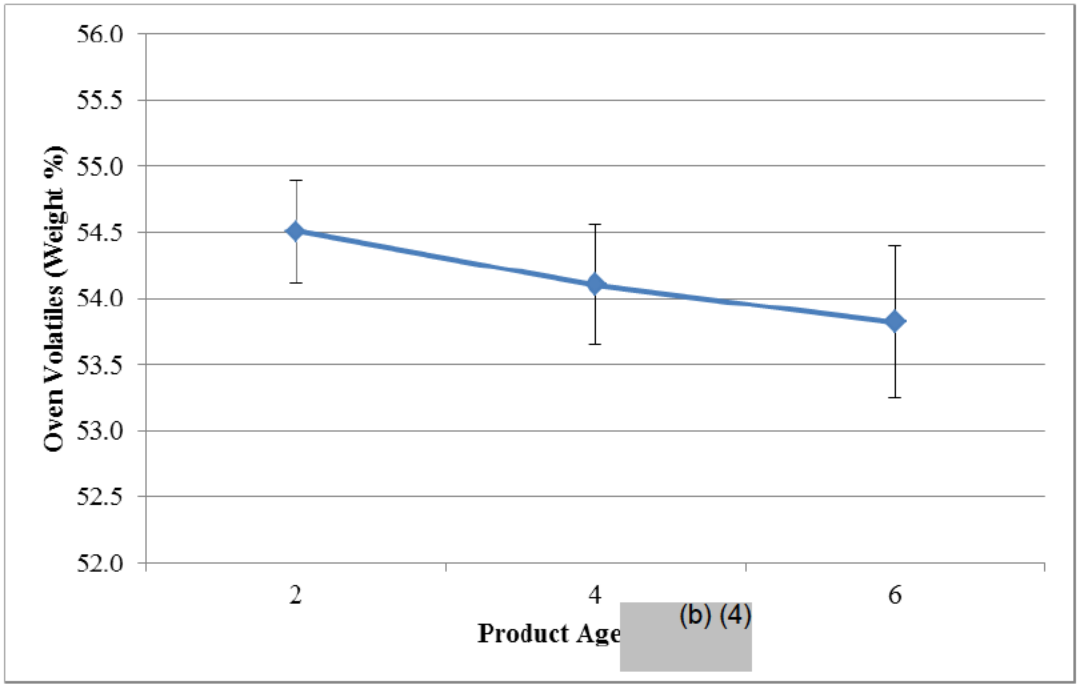
NOTE: Error bars represent the 95 % Confidence Interval.

Figure 7.2-5: Candidate Product 5-Lot Summary: pH Stability (b) (4)



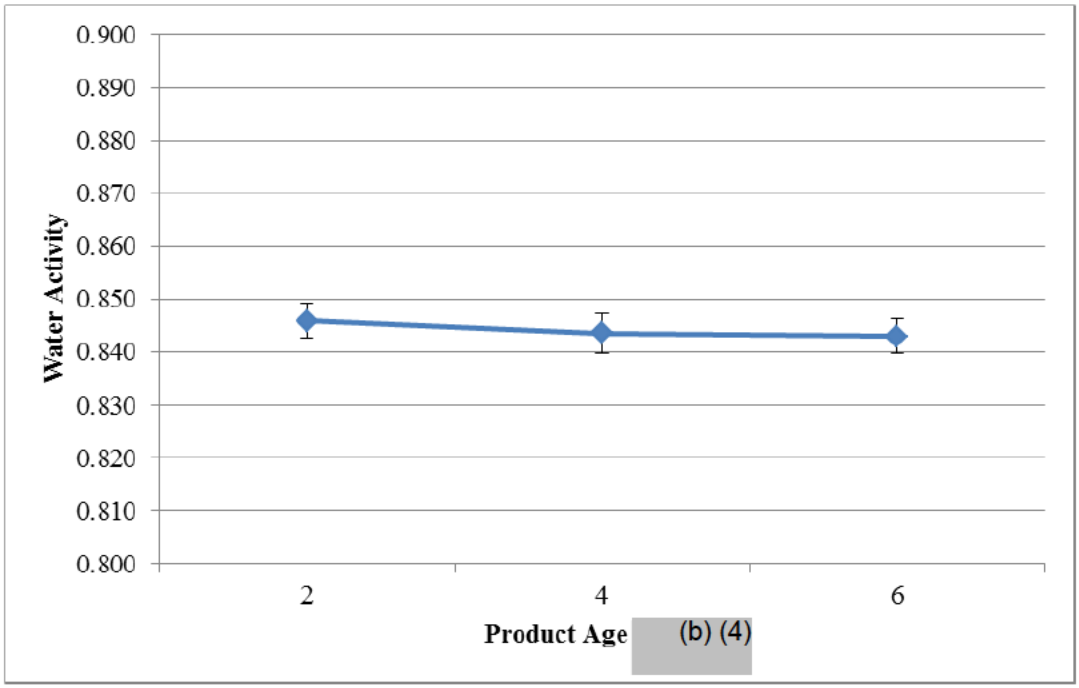
NOTE: Error bars represent the 95 % Confidence Interval.

Figure 7.2-6: Candidate Product 5-Lot Summary: Oven Volatiles Stability (b) (4)



NOTE: Error bars represent the 95 % Confidence Interval.

Figure 7.2-7: Candidate Product 5-Lot Summary: Water Activity Stability (b) (4)



NOTE: Error bars represent the 95 % Confidence Interval.