UREA BIO EXCIPIENT 2015 - 2018
LONG TERM STABILITY REPORT

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1. OVERVIEW:

The purpose of this Report is to analyze and conclude on the data obtained from the Long Term stability study of Urea Bio Excipient Grade. Testing intervals are designated by T_n, where n = the number of months on stability. Testing is performed every three months for the first year, every six months for the second year, and annually for each subsequent year in order to maintain that the manufactured product remains stable under the specified conditions and for the specified interval of time. The analysis of the compiled data may also aid in a re-evaluation of the retest date for the finished good product.

The data was analyzed utilizing a Shelf-Life Plot, which determines the point in time at which the slope would exceed the acceptance criteria. As long as the slope has a statistically significant difference from zero using a 95% confidence limit, an estimated time in months can be established at which the acceptance criteria will no longer be met, i.e. the Shelf Life. This allows BioSpectra to ensure that the product is stable over the time period in which it is part of the Stability Program. All quantitative data was analyzed using these methods. The data can be found in the Urea Real Time Stability Program binders.

This Long Term Stability analysis will assess the stability of 4 lots of Urea that were place on stability from 2012-2015. One lot per year was placed on stability and each study concluded three years later from 2015-2018. Each lot was analyzed for Biuret, Conductivity, Moisture, and Melting Range. Only quantitative data will be analyzed utilizing a Shelf life Plot. All lots met specification at each of the eight time points for Biuret and are considered acceptable.

2. DEFINITIONS:

CL: Control Limit, the average

UCL: Upper control limit, 3 sigma above the CL

LCL: Lower control limit, 3 sigma below the CL

OOT: Out Of Trend, this means that the material still meets control limits but was not in trend with the rest of the material.

OOS: Out of Specification, for the purpose of this stability analysis, OOS will mean that there is a point(s) that fall outside of the UCL or LCL.

3. SAMPLE DESIGNATION:

Samples initially placed on the Stability Program consisted of all process validation batches and one lot per year. Stability samples from each of these batches were packaged as Poly/Poly (P/P), Poly/Fiber (P/F), and Poly/Tyvek (T/P) in accordance with the Sampling Matrix SOP.

4. STORAGE:

The USP Packaging and Storage requirements for Urea are 15-30°C. Storage conditions have been continuously measured and recorded utilizing MadgeTech data loggers with regulated conditions for temperature (15-30°C) and humidity (monitor). Below are investigations for excursions from these conditions.

- SDI16-57 was issued for MadgeTech Data Logger #2 in the Stroudsburg Warehouse falling below the temperature specification. The heater was not turned on upon completion of maintenance in the warehouse. The lowest temperature reached was 12.73°C.
- SDI18-01 was issued for MadgeTech Data Logger #2, #5, and #6 in the Stroudsburg Warehouse falling below the temperature specification. The heaters were at the maximum temperature setting, due to persistently low outside temperature the heater were no able to maintain the temperature. The lowest temperature reached was 14.10°C.

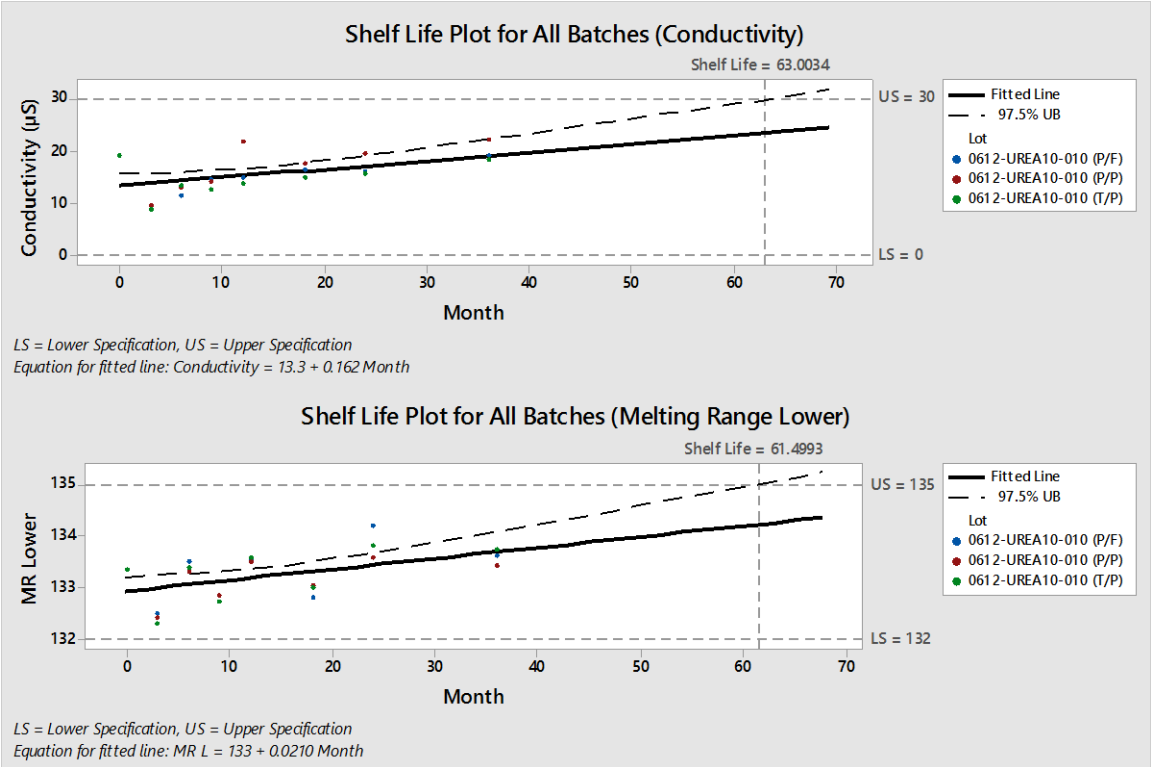
5. LOT ANALYSIS 2012:

The following graphs will evaluate the three packaging types of one lot of Urea placed on stability in 2012: 0612-UREA10-010. All packaging types were analyzed at each of the eight Long Term stability time points. However, moisture was only analyzed at T=24 and T=36 as this analysis was only added to the Stability Program for Urea in 2014. The following table shows the passing results for each packaging at the two time points it was analyzed, these results are considered acceptable in regards to the current 24 month retest date as well as the 36 month maximum expiration date assigned to this material.

TABLE 1. CONDUCTIVITY AND MELTING RANGE LOWER

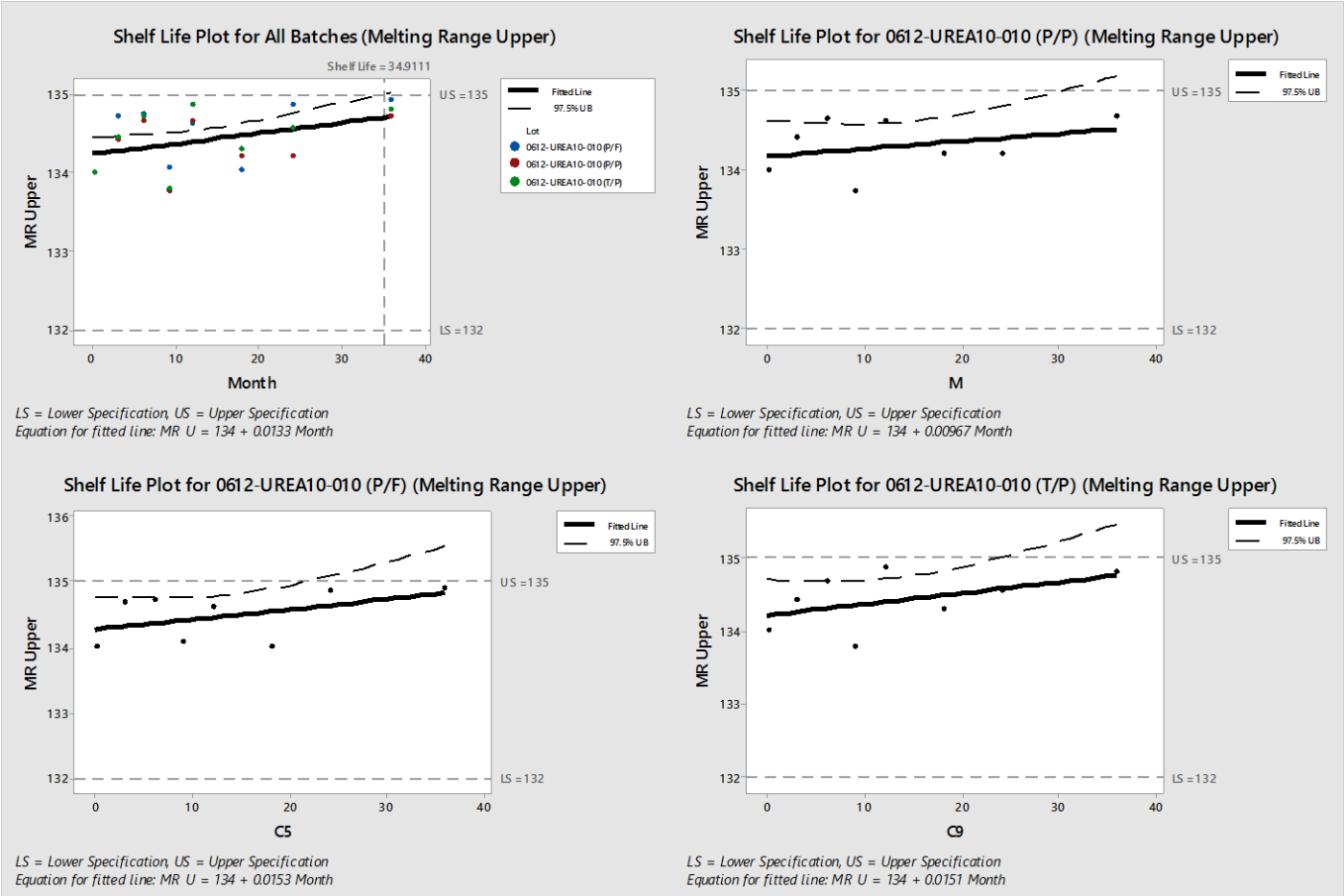
Lot Number	Packaging	Moisture Result	
		T=24	T=36
0612-UREA10-010	(P/P)	0.080%	0.040%
0612-UREA10-010	(P/F)	0.080%	0.040%
0612-UREA10-010	(T/P)	0.060%	0.020%

GRAPH 1. CONDUCTIVITY AND MELTING RANGE LOWER



Shelf lives of 63.0034 and 61.4993 months were predicted based on data for conductivity and melting range at the lower point respectively. The predicted shelf lives exceeds the current 24 month retest date as well as the 36 month maximum expiration date assigned to this material.

GRAPH 2. MELTING RANGE UPPER

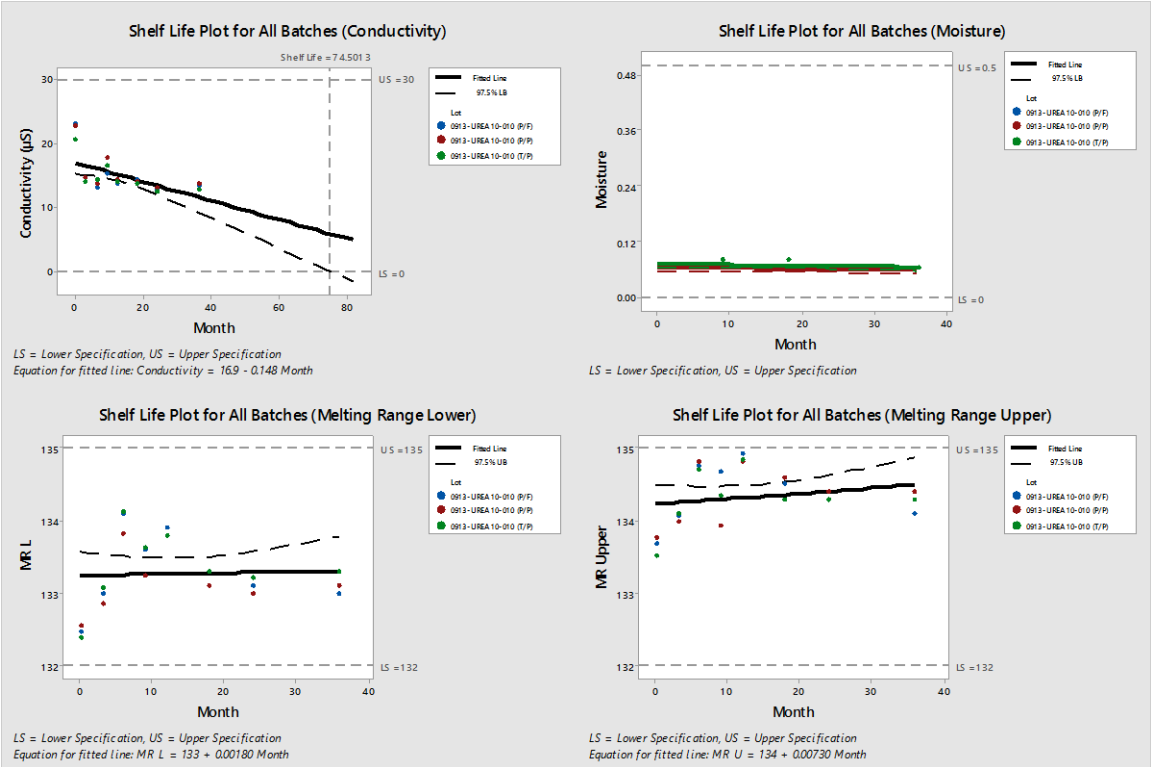


A Shelf life of 34.9111 months was predicted based on data for melting range at the upper time point. The predicted shelf life exceeds the current 24 month retest date, but does not exceed the 36 month maximum expiration date assigned to this material. However this shelf life is only predicted when the data for all three packagings are pooled together. Shelf life graphs for all three packagings when determined separately shows no predictable shelf life as the mean response slope is not significantly different from zero. This is observed as there is negligable degradation of the product shown from these analyses in the 36 month analysis timeframe.

6. LOT ANALYSIS 2013:

The following graphs will evaluate the three packaging types of one lot of Urea placed on stability in 2013: 0913-UREA10-010.

GRAPH 3. CONDUCTIVITY, MOISTURE, MELTING RANGE (LOWER AND UPPER)

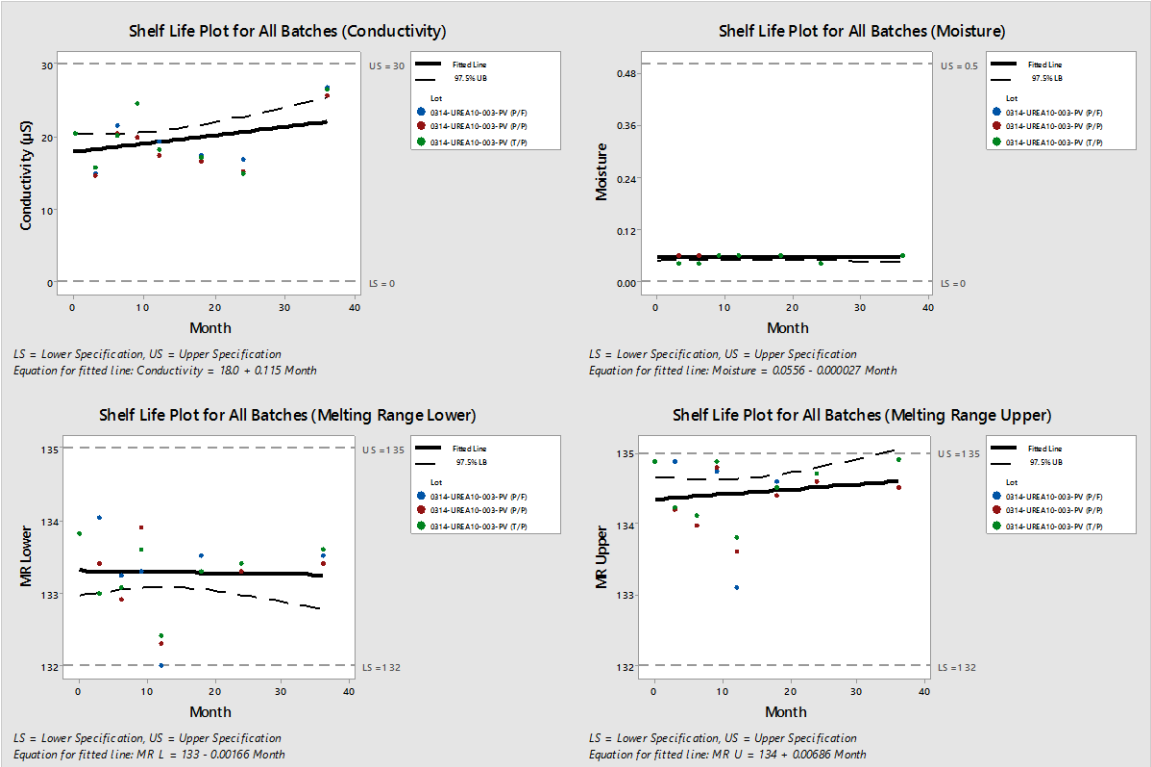


A Shelf life of 74.5013 months was predicted based on data for conductivity. The predicted shelf life exceeds the current 24 month retest date as well as the 36 month maximum expiration date assigned to this material. Data for moisture and melting range at the lower and upper points show no predictable shelf life as the mean response slope is not significantly different from zero. This is observed as there is negligable degradation of the product shown from these analyses in the 36 month analysis timeframe.

7. LOT ANALYSIS 2014:

The following graphs will evaluate the three packaging types of one lot of Urea placed on stability in 2014: 0314-UREA10-003-PV.

GRAPH 4. CONDUCTIVITY, MOISTURE, MELTING RANGE (LOWER AND UPPER)

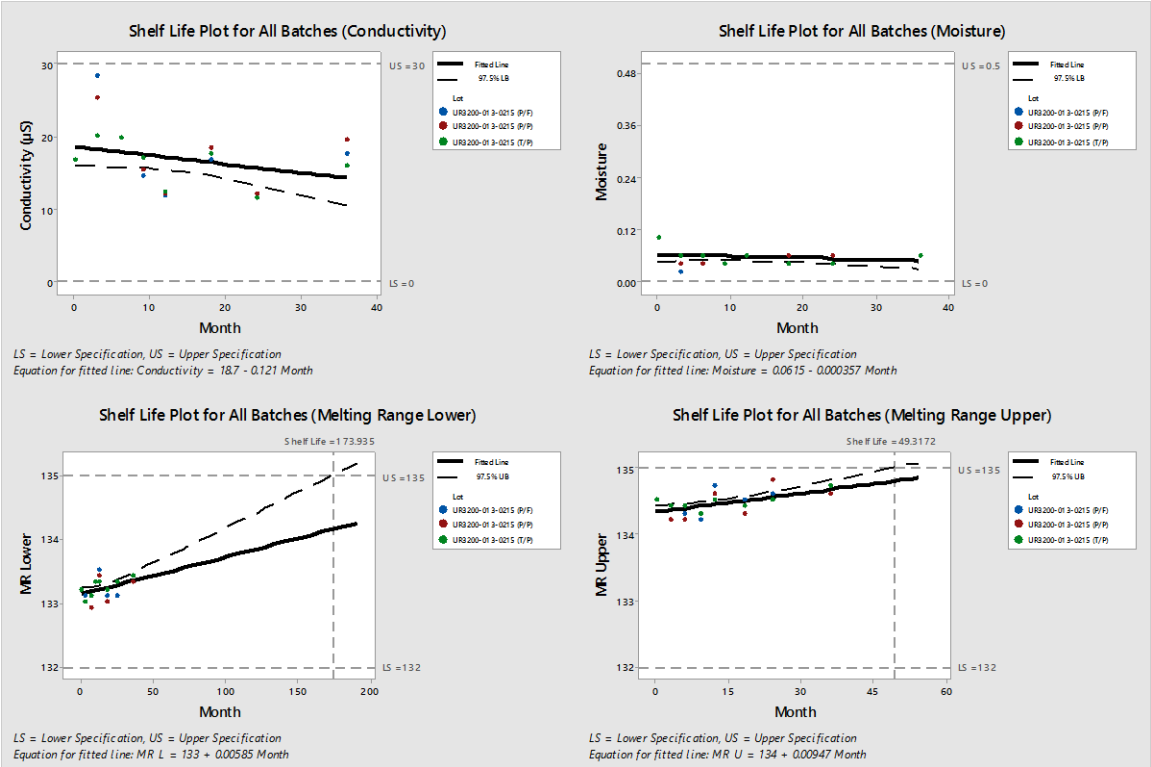


Data for conductivity, moisture and melting range at the lower and upper points show no predictable shelf life as the mean response slope is not significantly different from zero. This is observed as there is negligable degradation of the product shown from these analyses in the 36 month analysis timeframe.

8. LOT ANALYSIS 2015:

The following graphs will evaluate the three packaging types of one lot of Urea placed on stability in 2015: UR3200-013-0215.

GRAPH 5. CONDUCTIVITY, MOISTURE, MELTING RANGE (LOWER AND UPPER)



Data for conductivity and moisture show no predictable shelf life as the mean response slope is not significantly different from zero. This is observed as there is negligable degradation of the product shown from these analyses in the 36 month analysis timeframe. Shelf lives of 173.935 and 49.3172 months were predicted based on data for melting range at the lower and upper points respectively. The predicted shelf lives exceeds the current 24 month retest date as well as the 36 month maximum expiration date assigned to this material.

9. CONCLUSION:

Long Term Stability Data obtained for lots manufactured from 2012-2015 indicate that the material is stable for a minimum of 36 months. A 2 year retest date remains for this material since all lots at the 24 month data point have met specifications. Additional time after the two years may be given based on historical and current data up to one year after a retest has been conducted.

10. STATEMENT OF COMMITMENT:

BioSpectra is responsible for the following regarding Stability Data in this report:

- In the event that any stability analysis produces results found to be out of specification, the batch produced immediately before and after will be tested in full and analyzed in comparison with the batch in question.
    - This will serve to provide information to effectively ensure that the root cause of the investigation has not impacted the batch manufactured before or after the batch in question.
- If a stability analysis is found to be out of specification, the batch will be withdrawn from the market through communication with the Applicant and any additional customer. Additionally, an investigation will be conducted to determine the possible withdrawal of the batches produced before and after the batch in question.
- In the event that any out of specification results are confirmed, all authorized users of the material will be notified.

UREA BIO EXCIPIENT
REAL TIME STABILITY REPORT: UR3200-025-0616

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1. OVERVIEW:

The purpose of this report is to analyze the data obtained from the Real-Time Stability of Urea Bio Excipient Grade material manufactured at BioSpectra's Stroudsburg, PA facility. Samples were placed on the Stability Testing Program in June of 2016 to fulfil the requirements of placing one lot of manufactured material per year on the Stability Testing Program. Testing intervals are designated by T_n, where *n* represents the number of months on stability. Testing was performed for a total of thirty-six months: every three months for the first year, every six months for the second year, and annually for each subsequent year, in order to assure that the manufactured product remains stable under the specified conditions and for the specified interval of time. The analysis of the compiled data may be used to re-evaluate the retest period for future lots of manufactured material.

This Real-Time Stability Report assesses the stability of one lot of Urea, Bio Excipient that completed three years of long-term stability in June 2019. The stability study included the following analyses: Biuret, Conductivity, Moisture and Melting Range. In November of 2017, Assay and Impurities were added as a Stability Analysis for Urea. The result obtained for Organic Impurities accounts for any biuret within the product. Biuret was removed from the stability requirements between T_9 and T_{18} timepoints. Results from all analyses are summarized in Table 2, and Shelf-Life Plots have been predicted for all quantitative analyses. Shelf-Life Plots determine the point in time at which the slope would exceed the acceptance criteria. As long as the slope has a statistically significant difference from zero using a 95% confidence limit, an estimated time in months can be established at which the acceptance criteria will no longer be met, i.e. the Predicted Shelf-Life. This allows BioSpectra to ensure that the product will be stable over the time period in which it is part of the Stability Testing Program.

2. REFERENCES:

2.1. Current USP
2.2. ICH Q1
2.3. Stability Testing Program
2.4. Stability Inventory

3. SAMPLE DESIGNATION:

Samples placed on the Stability Testing Program consisted of one lot of Urea. Stability samples from this batch were put into four different packaging configurations. These samples were packaged in accordance with the Stability Inventory SOP. Reference Table 1, below, for packaging configurations and descriptions. The type of packaging utilized in this stability study was based on BioSpectra final packaging offered to the customer.

TABLE 1: PACKAGING DETAILS

Packaging Configuration	Packaging Description
Poly/Fiber (P/F)	Samples are packaged into small poly bags and sealed with a ziptie. All individual samples are then placed into a fiber drum, along with a 4-unit desiccant.
Poly/Poly (P/P)	Samples are packaged into small poly bags and sealed with a ziptie. All individual samples are then placed into a poly drum.
Tyvek/Poly (T/P)	Samples are packaged into small tyvek bags and sealed with a ziptie. All individual samples are then placed into a poly drum, along with a 5x8-unit desiccant.
2 Tyvek/Poly (2T/P)	Samples are packaged into small tyvek bags and sealed with a ziptie. All individual samples are then placed into a larger tyvek bag with a 5x8-unit desiccant. This bag will then get placed into a poly drum.

4. STORAGE:

Samples were placed on stability in BioSpectra's Stroudsburg PA facility Stability Area, located in the quarantine area of the Warehouse. The USP Packaging and Storage requirements for Urea are 15-30°C. Storage conditions were continuously measured and recorded utilizing MadgeTech data loggers with regulated conditions for temperature (15-30°C) and humidity (monitor). The maximum temperature of the warehouse during the stability study was 28.14°C, and the minimum temperature of the warehouse was 12.63°C. See Section 5 for the Discrepancy Investigations initiated for temperature excursions.

5. INVESTIGATIONS:

5.1. SDI16-57 was initiated for temperatures dropping below the minimum storage temperature of 15°C. The temperature excursion had no impact on the Urea stability samples, as the next time point, T_6, was pulled and tested without issue.

5.2. SDI18-01 was initiated for temperatures dropping below the minimum storage temperature of 15°C. The temperature excursion had no impact on the Urea stability samples, as the next time point, T_{24} was pulled and tested without issue.

6. LOT EVALUATION:

TABLE 2: ALL-INCLUSIVE STABILITY DATA

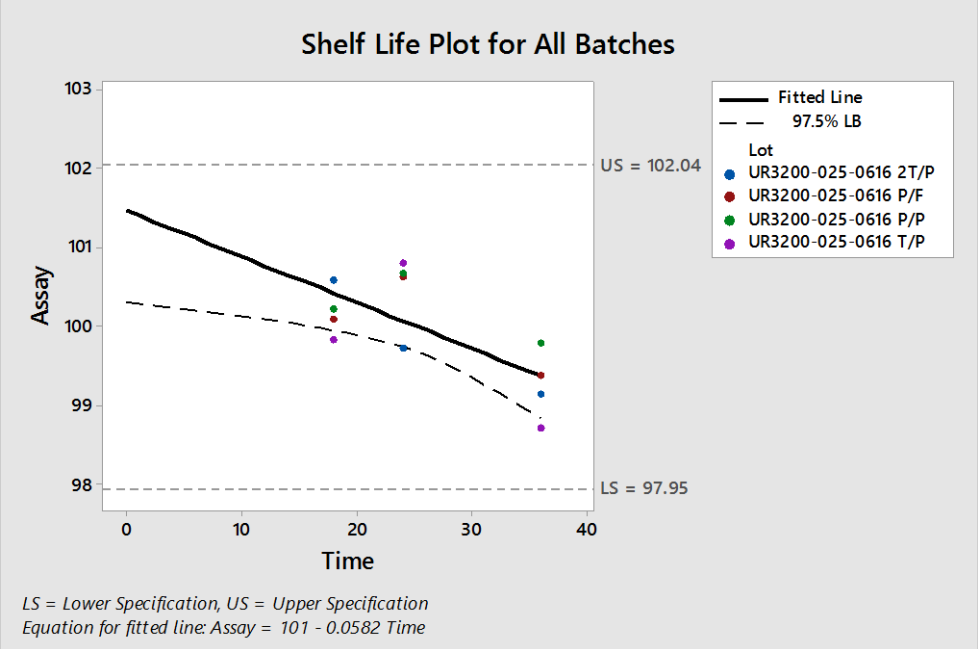
Urea Bio Excipient Stability Data										
Lot Number	**Analysis**	**Specification**	**T_0[1]**	**T_3**	**T_6**	**T_9**	**T_{12}**	**T_{18}**	**T_{24}**	**T_{36}**
UR3200-025-0616 P/F	Assay	98.0-102.0%	*Not yet required*	*Not yet required*	*Not yet required*	*Not yet required*	*Not yet required*	100.07%	100.62%	99.37%
	Biuret	0.1% max.	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	*No longer required*	*No longer required*	*No longer required*
	Conductivity	30µS/cm max.	18.71µS/cm @ 19.8°C	12.12µS/cm @ 22.1°C	11.8µS/cm @ 22.3°C	20.3µS/cm @ 23.4°C	14.48µS/cm @ 23.8°C	16.0 µS/cm @ 21.3°C	14.0 µS/cm @ 20.5°C	16.3µS/cm @ 26.3°C
	Moisture	0.5% max.	0.080%	0.040%	0.060%	0.060%	0.060%	0.060%	0.040%	0.060%
	Melting Range	132-135°C	133.1-134.5°C	133.1-134.3°C	132.8-134.2°C	133.6-134.7°C	133.2-134.4°C	133.4-134.7°C	133.3-134.5°C	133.1-134.8°C
	Impurities	Organic <0.1%	*Not yet required*	*Not yet required*	*Not yet required*	*Not yet required*	*Not yet required*	0.05%	<0.1%	<0.1%
		Total <2.0%	*Not yet required*	*Not yet required*	*Not yet required*	*Not yet required*	*Not yet required*	<2.0%	<2.0%	<2.0%
		Unspecified <0.1%	*Not yet required*	*Not yet required*	*Not yet required*	*Not yet required*	*Not yet required*	0.000%	<0.1%	<0.1%
UR3200-025-0616 P/P	Assay	98.0-102.0%	*Not yet required*	*Not yet required*	*Not yet required*	*Not yet required*	*Not yet required*	100.21%	100.66%	99.77%
	Biuret	0.1% max.	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	*No longer required*	*No longer required*	*No longer required*
	Conductivity	30µS/cm max.	18.71µS/cm @ 19.8°C	12.08µS/cm @ 21.7°C	12.0µS/cm @ 22.4°C	18.8µS/cm @ 23.8°C	13.34µS/cm @ 23.7°C	16.3µS/cm @ 21.8	12.2µS/cm @ 20.7°C	14.5µS/cm @ 26.4°C
	Moisture	0.5% max.	0.080%	0.060%	0.060%	0.060%	0.040%	0.060%	0.040%	0.060%
	Melting Range	132-135°C	133.1-134.5°C	132.8-134.2°C	133.4-134.7°C	133.5-134.8°C	133.4-134.6°C	133.0-134.4°C	133.3-134.5°C	133.2-134.6°C
	Impurities	Organic <0.1%	*Not yet required*	*Not yet required*	*Not yet required*	*Not yet required*	*Not yet required*	0.06%	<0.1%	<0.1%
		Total <2.0%	*Not yet required*	*Not yet required*	*Not yet required*	*Not yet required*	*Not yet required*	<2.0%	<2.0%	<2.0%
		Unspecified <0.1%	*Not yet required*	*Not yet required*	*Not yet required*	*Not yet required*	*Not yet required*	0.000%	<0.1%	<0.1%
UR3200-025-0616 T/P	Assay	98.0-102.0%	*Not yet required*	*Not yet required*	*Not yet required*	*Not yet required*	*Not yet required*	99.82%	100.78%	98.71%
	Biuret	0.1% max.	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	*No longer required*	*No longer required*	*No longer required*
	Conductivity	30µS/cm max.	18.71µS/cm @ 19.8°C	12.64µS/cm @ 22.2°C	11.6µS/cm @ 22.0°C	15.2µS/cm @ 23.7°C	12.28µS/cm @ 23.8°C	14.3µS/cm @ 22.6°C	10.2µS/cm @ 20.3°C	15.0µS/cm @ 26.1°C
	Moisture	0.5% max.	0.080%	0.040%	0.040%	0.060%	0.040%	0.060%	0.080%	0.040%
	Melting Range	132-135°C	133.1-134.5°C	133.1-134.4°C	133.4-134.5°C	133.6-134.8°C	133.3-134.7°C	133.3-134.6°C	133.4-134.5°C	132.6-134.2°C
	Impurities	Organic <0.1%	*Not yet required*	*Not yet required*	*Not yet required*	*Not yet required*	*Not yet required*	0.05%	<0.1%	<0.1%
		Total <2.0%	*Not yet required*	*Not yet required*	*Not yet required*	*Not yet required*	*Not yet required*	<2.0%	<2.0%	<2.0%
		Unspecified <0.1%	*Not yet required*	*Not yet required*	*Not yet required*	*Not yet required*	*Not yet required*	0.000%	<0.1%	<0.1%

[1] Finished Goods testing was transcribed to summary sheets and will be used for T=0, as the testing is equivalent.

Urea Bio Excipient Stability Data										
Lot Number	**Analysis**	**Specification**	**T_0[1]**	**T_3**	**T_6**	**T_9**	**T_{12}**	**T_{18}**	**T_{24}**	**T_{36}**
UR3200-025-0616 2T/P	Assay	98.0-102.0%	*Not yet required*	*Not yet required*	*Not yet required*	*Not yet required*	*Not yet required*	100.58%	99.72%	99.14%
	Biuret	0.1% max.	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	*No longer required*	*No longer required*	*No longer required*
	Conductivity	30µS/cm max.	18.71µS/cm @ 19.8°C	11.33µS/cm @ 21.6°C	13.0µS/cm @ 21.8°C	17.0µS/cm @ 24.2°C	14.03µS/cm @ 23.7°C	13.8µS/cm @ 21.0°C	12.4µS/cm @ 20.3°C	14.5µS/cm @ 25.6°C
	Moisture	0.5% max.	0.080%	0.060%	0.040%	0.060%	0.060%	0.060%	0.060%	0.060%
	Melting Range	132-135°C	133.1-134.5°C	133.0-134.3°C	133.3-134.5°C	133.3-134.6°C	133.4-134.6°C	133.3-134.6°C	133.2-134.4°C	133.2-134.9°C
	Impurities	Organic <0.1%	*Not yet required*	*Not yet required*	*Not yet required*	*Not yet required*	*Not yet required*	0.05%	<0.1%	<0.1%
		Total <2.0%	*Not yet required*	*Not yet required*	*Not yet required*	*Not yet required*	*Not yet required*	<2.0%	<2.0%	<2.0%
		Unspecified <0.1%	*Not yet required*	*Not yet required*	*Not yet required*	*Not yet required*	*Not yet required*	0.000%	<0.1%	<0.1%

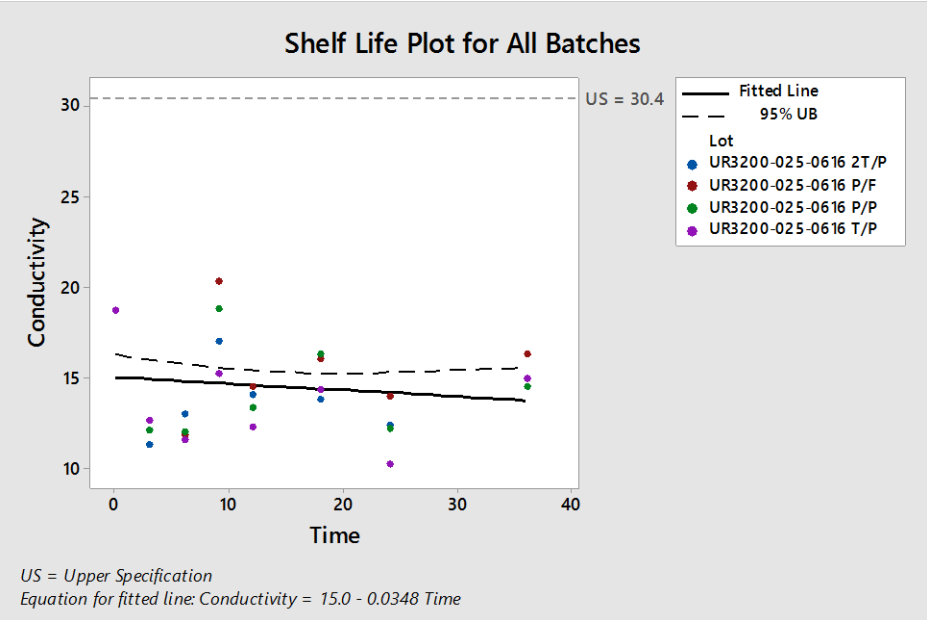
[1]Finished Goods testing was transcribed to summary sheets and will be used for T=0, as the testing is equivalent.

GRAPH 1: SHELF LIFE PLOT FOR ASSAY (%)



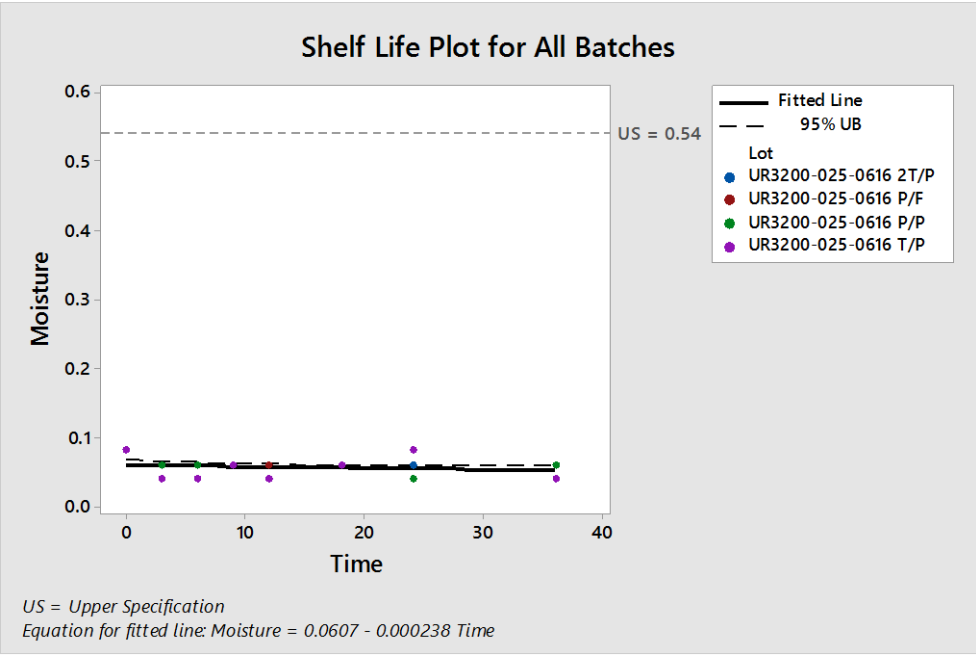
No Shelf-Life is able to be determined for Assay, as the mean slope response is not significantly different from zero. There is no impact to the product or currently assigned expiration of this material.

GRAPH 2: SHELF LIFE PLOT FOR CONDUCTIVITY



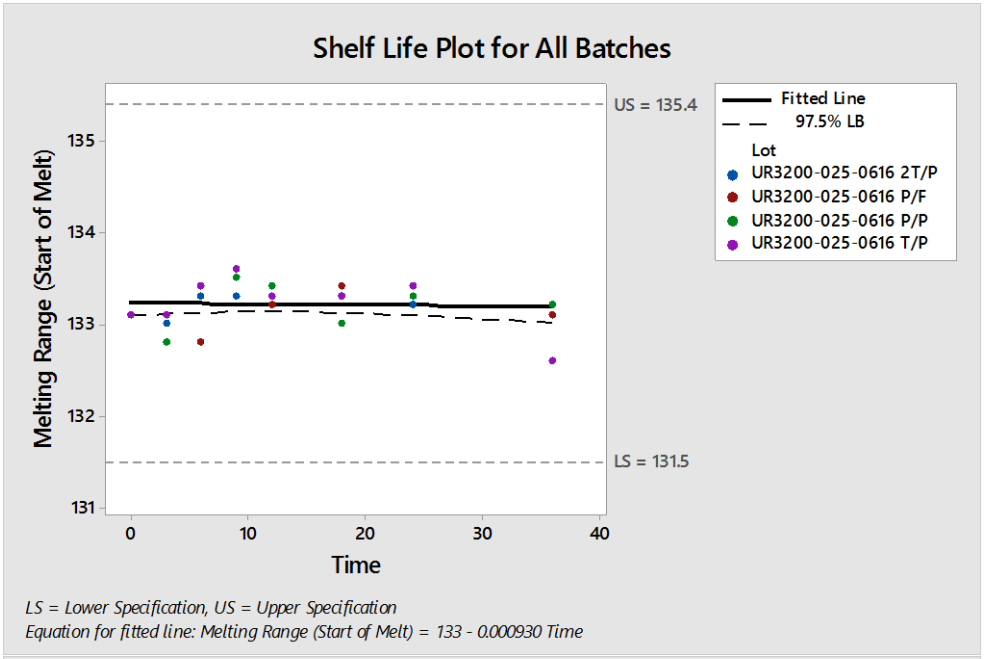
No Shelf-Life is able to be determined for Conductivity, as the mean slope is not significantly different from zero. There is no impact to the product or currently assigned expiration of this material.

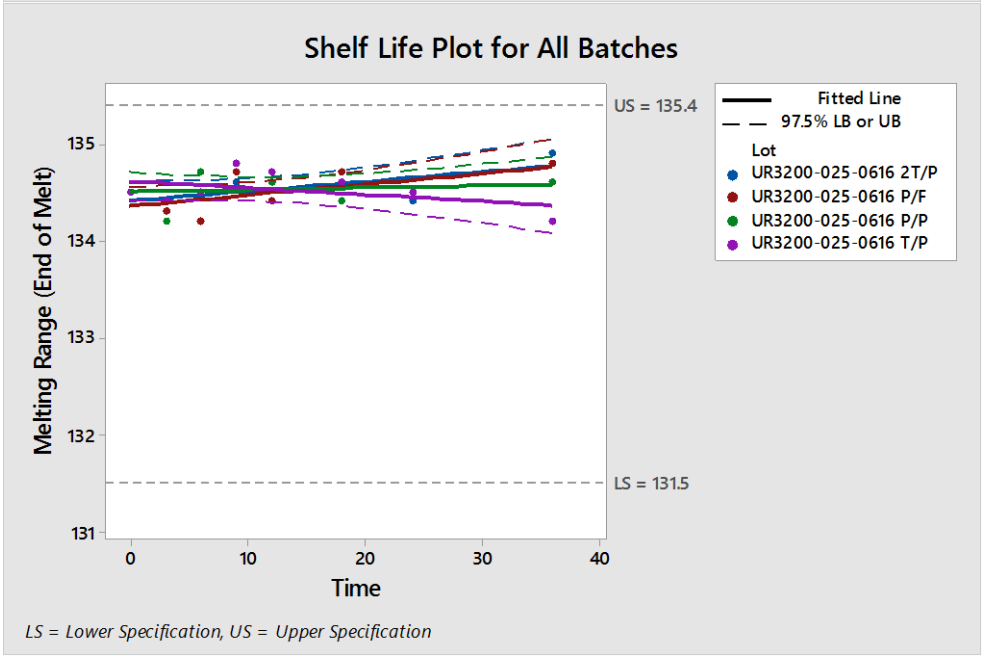
GRAPH 3: SHELF LIFE PLOT FOR MOISTURE (%)



No Shelf-Life is able to be determined for Moisture, as the mean slope is not significantly different from zero. There is no impact to the product or currently assigned expiration of this material.

GRAPHS 4 AND 5: SHELF LIFE PLOT FOR MELTING RANGE





No Shelf-Life is able to be determined for Melting Range, as the mean slope is not significantly different from zero. There is no impact to the product or currently assigned expiration of this material.

7. CONCLUSION:

All data met the specifications set forth in the Stability Testing Program. In accordance with ICH Q1E 2.4.2.1, the retest date may be proposed for up to 2*x* where *x* is the period covered by long-term stability data, but should be no more than 12 months beyond. The data obtained during this stability study indicates that Urea Bio Excipient material is stabile for 36 months in Tyvek/Poly, Poly/Poly, Poly/Fiber, and 2Tyvek/Poly packagings. The assigned re-test date of manufactured Urea Bio Excipient material will remain at 24 months unless otherwise requested on a lot-by-lot basis.

8. STATEMENT OF COMMITMENT:

8.1. BioSpectra is responsible for the following regarding Stability Data in this report:

8.1.1. In the event that any stability analysis produces results found to be out of specification, the batch produced immediately before and after will be tested in full and analyzed in comparison with the batch in question.

8.1.1.1. This will serve to provide information to effectively ensure that the root cause of the investigation has not impacted the batch manufactured before or after the batch in question.

8.1.2. If a stability analysis is found to be out of specification, the batch will be withdrawn from the market through communication with the Applicant and any additional customer. Additionally, an investigation will be conducted to determine the possible withdrawal of the batches produced before and after the batch in question.

8.1.3. In the event that any out of specification results are confirmed, all authorized users of the material will be notified.