BIOSPECTRA
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UREA 6M SOLUTION 2021-2022 VALIDATION LOTS 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 6M Solution. 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.

This long-term analysis will assess the stability data of Urea 6M Solution validation lots UREA-0121-00041-PV, UREA-0121-00042-PV, UREA-0121-00045-PV and UREA-0122-00003-PV that completed thirty-six (36) months of long-term stability in December 2024 and January 2025. This study includes the analyses in Table 1 Below. Appearance, Identification (IR), Molarity, and pH (25°C). The Stability Study is based on evaluating the material against Finished Good Specifications only with the exception of Trace Metals. Results from all analyses are summarized in Table 4 through 7.

TABLE 1: STABILITY SPECIFICATIONS

Analysis	Specification
Appearance	Colorless Liquid
Identification (IR)	Conforms to Standard
Molarity	5.8 – 6.2M
pH (25°C)	7 - 10

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 specifications for this stability study are established in accordance with UREA-3120 Urea 6M Solution, GMP Excipient Specifications, BSI-SPC-0287. The study is used to trend the data to determine if there is any significant change over the course of the study to establish the shelf life of the product. This study will be used to establish shelf life for all product codes of Urea 6M Solution. The following product code is commercially available:

- UREA-3120

2. REFERENCES:

2.1. BSI-SPC-0287, UREA-3120 Urea 6M Solution, GMP Excipient Specifications
2.2. BSI-SOP-0136, Stability Testing Program
2.3. BSI-SOP-0146, Stability Inventory
2.4. Current USP
2.5. ICH Q1E

3. SAMPLE DESIGNATION:

3.1. Samples initially placed on the stability program for long term testing consisted of four lots of Urea 6M solutions. Stability samples from these lots were put into an HDPE bottle (Black Bottle with Black Cap) packaging configuration. The samples were packaged in accordance with the Stability Inventory SOP, BSI-SOP-0146. Reference Table 2 for packaging configuration and description. The type of packaging utilized in this stability study was based on BioSpectra's packaging configuration offered to the customer.

TABLE 2: PACKAGING DETAILS

Packaging Configuration	Packaging Description
Black Bottle with Black Cap (HDPE Bottle)	Samples are packaged into a HDPE Lab Screw-Top Bottle

4. STORAGE:

4.1. The Packaging and Storage requirements for Urea 6M Solution are to be in a tightly closed container and stored in a dry, well-ventilated area away from incompatible substances. For the long term study, the samples were stored in the Real Time Stability Chamber H03SC01, from December 2021 up to January 2025 at the Bangor, PA facility. Storage conditions have been continuously measured and recorded utilizing MadgeTech data loggers with regulated conditions for temperature (25°C ±2°C), mean kinetic temperature (monitor) and relative humidity (60% ±5%). Maximum and minimum values that are outside the limits for temperature and humidity are due to opening the door of the chamber as explained in the Temperature and Humidity Monitoring Assessments for the chamber. The storage conditions for the time period of this study are detailed in Table 3. Section 5 will include any excursions from these conditions that resulted in an investigation. The remaining samples for these lots will remain in the Real Time Stability Chamber until they are scheduled to be tested, and the temperature and humidity will continue to be monitored.

TABLE 3: STORAGE CONDITIONS

Condition	Specification	Value
Minimum Temperature	25°C ±2°C	21.81°C
Maximum Temperature		26.20°C
Average Temperature		25.41°C
Mean Kinetic Temperature	Monitor	25.41°C
Minimum Humidity	60%RH ±5%RH	32.4%
Maximum Humidity		80.5%
Average Humidity		61.2%

5. INVESTIGATIONS:

5.1. **BDI22-61**: This discrepancy investigation documents missing data points between 01/28/22 and 02/09/22 for MadgeTech data loggers in the Real Time Stability Chamber. The backup analog chart recorders were reviewed, and there were no temperature or humidity deviations recorded during this time period. The MadgeTech data loggers were evaluated and reset, and recorded without incident since this event. It was determined that there was no effect on the samples at this time.

5.2. **BDI22-138**: This discrepancy investigation documents out of specification (low) humidity values for the Real Time Stability Chamber. It was determined that a water valve to the humidifier was closed accidentally, which resulted in an alarm warning that the chamber was experiencing lower humidity than for the setpoint. The valve was labeled by the preventative maintenance team to eliminate future issues with this valve. There was no impact on the stability samples due to the excursion being brief (less than 5 hours).

5.3. **BDI22-275:** This discrepancy documents the July 2022 temperature and humidity assessments being completed in excess of a month of the data being downloaded. There was no impact to the stability samples as all data downloaded was within specifications.

5.4. **BDI24-13**: Out of range humidity for the Long-Term Stability Chamber H03SC01 caused by improper work order completion to prevent water leaking from the stability chamber. On 1/15/24 while conducting a maintenance walkthrough of the Bangor facility water was observed on the floor of room H03RM01. The issue was found to be a faulty pump and later repaired. There was no impact to the current list of materials in the stability chamber.

5.5. **BDI24-126:** Out of specification humidity reading of 54.4% RH was observed on 8/15/24 at 2222. After further investigation, it was found that the main 20-amp fuse for the stability chamber had blown. After the fuse was replaced, the temperature and humidity returned to within specifications. The minimum temperature was 21.81°C and the minimum humidity was 50.3% RH. There was no impact to the samples stored in the chamber.

6. LOT EVALUATION:

TABLE 4: RESULT OF LONG-TERM STABILITY ANALYSES FOR UREA-0121-00041-PV

Time Point	Analyses/Specifications			
	Appearance	Identification (IR)	Molarity	pH @ 25°C
	Colorless Liquid	Conforms to Standard	5.8 – 6.2M	7 – 10
T_0	Colorless Liquid	Conforms to Standard	5.9M	7.70
T_3	Colorless Liquid	Conforms to Standard	5.9M	8.95
T_6	Colorless Liquid	Conforms to Standard	5.9M	9.28
T_9	Colorless Liquid	Conforms to Standard	6.0M	9.46
T_{12}	Colorless Liquid	Conforms to Standard	5.9M	9.42
T_{18}	Colorless Liquid	Conforms to Standard	6.0M	9.47
T_{24}	Colorless Liquid	Conforms to Standard	5.8M	9.51
T_{36}	Colorless Liquid	Conforms to Standard	5.9M	9.48

TABLE 5: RESULT OF LONG-TERM STABILITY ANALYSES FOR UREA-0121-00042-PV

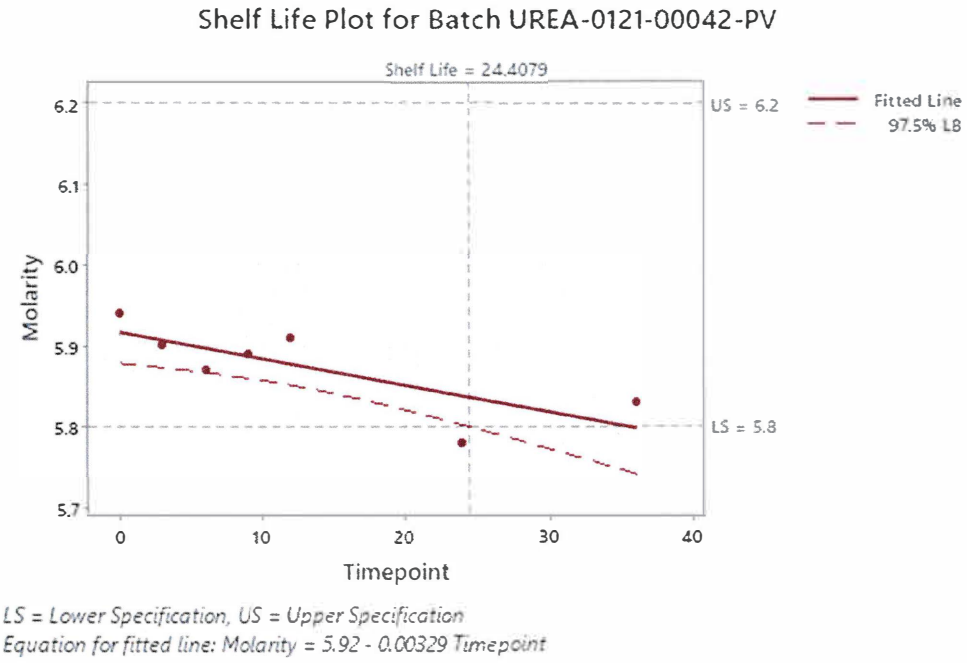
Time Point	Analyses/Specifications			
	Appearance	Identification (IR)	Molarity	pH @ 25°C
	Colorless Liquid	Conforms to Standard	5.8 – 6.2M	7 – 10
T_0	Colorless Liquid	Conforms to Standard	5.9M	7.30
T_3	Colorless Liquid	Conforms to Standard	5.9M	8.96
T_6	Colorless Liquid	Conforms to Standard	5.9M	9.27
T_9	Colorless Liquid	Conforms to Standard	5.9M	9.38
T_{12}	Colorless Liquid	Conforms to Standard	5.9M	9.41
T_{18}	Colorless Liquid	Conforms to Standard	5.9M	9.51
T_{24}	Colorless Liquid	Conforms to Standard	5.8M	9.50
T_{36}	Colorless Liquid	Conforms to Standard	5.8M	9.49

TABLE 6: RESULT OF LONG-TERM STABILITY ANALYSES FOR UREA-0121-00045-PV

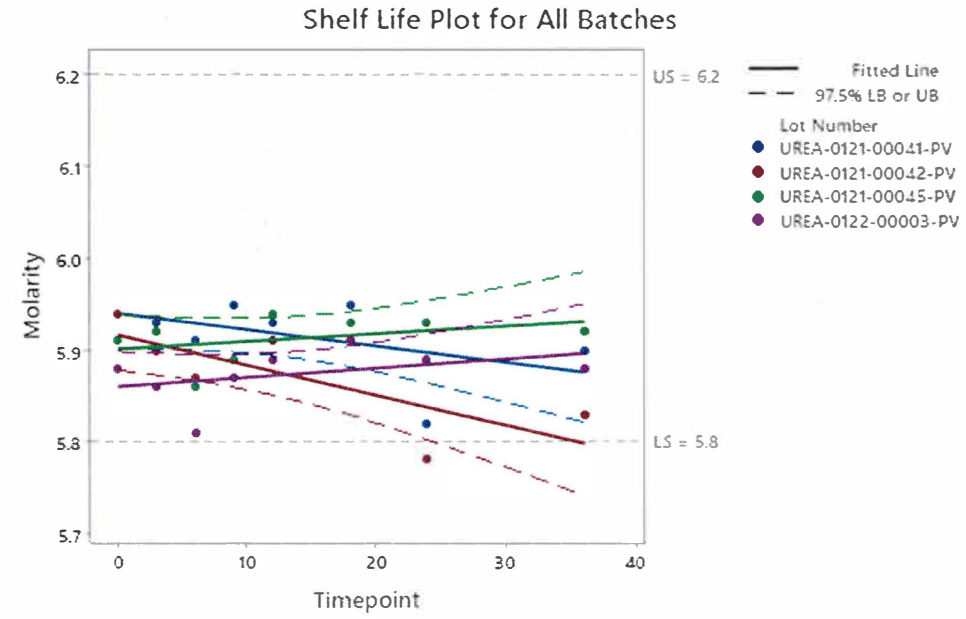
Time Point	Analyses/Specifications			
	Appearance	Identification (IR)	Molarity	pH @ 25°C
	Colorless Liquid	Conforms to Standard	5.8 – 6.2M	7 – 10
T_0	Colorless Liquid	Conforms to Standard	5.9M	7.81
T_3	Colorless Liquid	Conforms to Standard	5.9M	8.80
T_6	Colorless Liquid	Conforms to Standard	5.9M	9.25
T_9	Colorless Liquid	Conforms to Standard	5.9M	9.27
T_{12}	Colorless Liquid	Conforms to Standard	5.9M	9.45
T_{18}	Colorless Liquid	Conforms to Standard	5.9M	9.46
T_{24}	Colorless Liquid	Conforms to Standard	5.9M	9.48
T_{36}	Colorless Liquid	Conforms to Standard	5.9M	9.53

TABLE 7: RESULT OF LONG-TERM STABILITY ANALYSES FOR UREA-0122-00003-PV

Time Point	Analyses/Specifications			
	Appearance	Identification (IR)	Molarity	pH @ 25°C
	Colorless Liquid	Conforms to Standard	5.8 – 6.2M	7 – 10
T_0	Colorless Liquid	Conforms to Standard	5.9M	7.89
T_3	Colorless Liquid	Conforms to Standard	5.9M	8.89
T_6	Colorless Liquid	Conforms to Standard	5.8M	9.21
T_9	Colorless Liquid	Conforms to Standard	5.9M	9.32
T_{12}	Colorless Liquid	Conforms to Standard	5.9M	9.45
T_{18}	Colorless Liquid	Conforms to Standard	5.9M	9.52
T_{24}	Colorless Liquid	Conforms to Standard	5.9M	9.49
T_{36}	Colorless Liquid	Conforms to Standard	5.9M	9.53



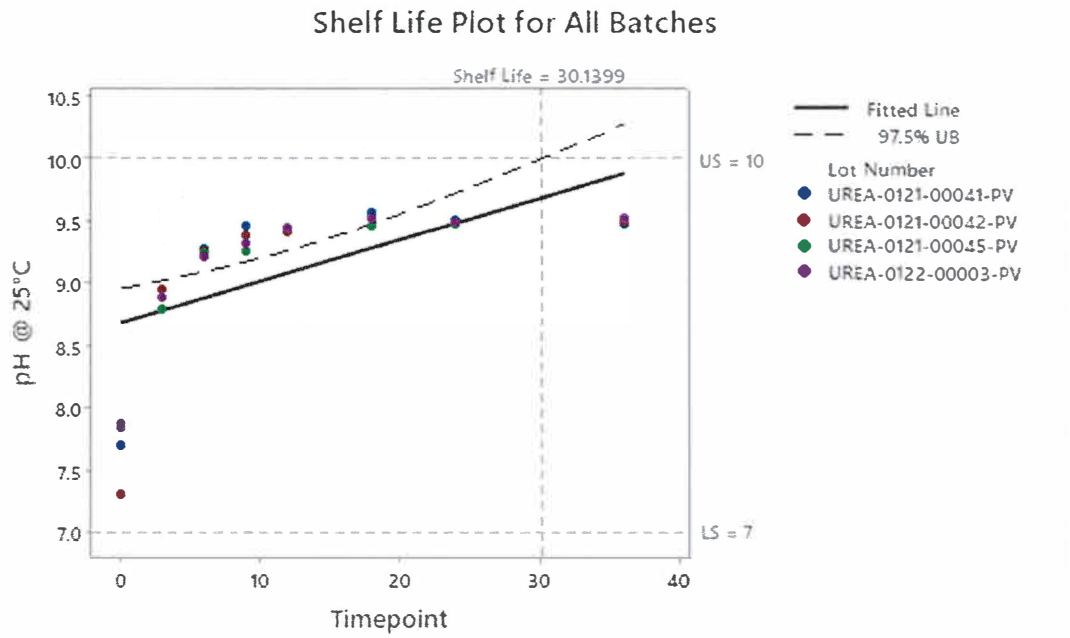
LS = Lower Specification, US = Upper Specification
Equation for fitted line: Molarity = 5.92 - 0.00329 Timepoint



LS = Lower Specification, US = Upper Specification

GRAPH 1: REAL TIME MOLARITY

The predicted shelf-life for Molarity for Batch UREA-0121-00042-PV was determined to be 24.4079 months at the T=36-month time interval. All timepoint intervals did pass specification up to the T=36 sample. The shelf-life is defined as the time period in which you may be 95% confident that at least 50% of the response is within the required limits of specifications. All data up to the 36-month time point has met the required specification.



LS = Lower Specification, US = Upper Specification
Equation for fitted line: pH @ 25°C = 8.69 + 0.0331 Timepoint

GRAPH 2: REAL TIME PH (5%)

The predicted shelf-life for pH @ 25°C was determined to be 30.1399 months at the T=36-month time interval. All timepoint intervals did pass specification up to the T=36 sample. The shelf-life is defined as the time period in which you may be 95% confident that at least 50% of the response is within the required limits of specifications. All data up to the 36-month time point has met the required specification.

7. CONCLUSION:

All data met the specifications set forth in the Stability Testing Program. In accordance with ICH Q1E, the retest date may be proposed for up to 2x, where x is the period covered by long time stability data, but should be no more than 12 months beyond for long term conditions. Long Term Stability Data based on the Finished Good specifications, with the exception of Trace Metals, displayed in this report up to 36 months for Urea 6M Solution manufactured at BioSpectra in the Bangor, PA facility, along with the predicted shelf-life plots, would support a retest date of 24 months with an expiration date of 36 months.

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.

8.1.2. 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.

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

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