

ACCELERATED STABILITY REPORT:
UREA BIO ACTIVE 2017

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1. OVERVIEW:

The purpose of this report is to analyze the data obtained from the accelerated stability of Urea Bio Active Grade manufactured in API Suite 1, Room E05 of BioSpectra's Bangor, PA facility. Samples were initially placed on the stability program in May 2016 consisting of four Urea Active Process Validation batches with each lot contained in one pail. Analysis was conducted on a monthly basis for a total of six months in order to assure that the manufactured product remains stable under the specified conditions and for the specified interval of time.

The data was analyzed utilizing Shelf Life Plots, which show process performance using continuous data, in this case, time in months. 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 the individual Analytical Summary Sheets for analysis of the product, as well as attached to this report as a supporting document in the ensur document management system.

This accelerated Stability report assesses the stability of four lots of Urea Bio Active Grade that completed the accelerated stability testing intervals in February of 2017. The study included the following analysis: Biuret, Conductivity, Moisture, Melting Range and Loss on Drying as determined by the stability indicating report. Biuret is a qualitative test and all results met requirements. These results will not be analyzed in the graphs below.

2. REFERENCES:

- 2.1. Current USP
- 2.2. ICH Q1E: Evaluation for Stability Data

3. DEFINITIONS:

- 3.1. US: Upper Specification
- 3.2. LS: Lower Specification
- 3.3. T: Time in months

4. SAMPLE DESIGNATION:

Samples initially placed on the stability program consisted of four Urea Bio Active Process Validation batches. Stability samples from each of the batches were put into a round poly pail lined with two poly liners (Polyethylene/Polyethylene), with the outer liner being goose-neck tied closed. These batches were placed on stability in the Darwin Accelerated Stability Chamber located in the BioSpectra

Bangor, PA facility. The type of packaging utilized in the accelerated stability samples was based on BioSpectra packaging.

5. STORAGE:

Storage conditions have been continuously monitored and recorded. The temperature and humidity were monitored continuously utilizing a chart recorder and MadgeTech data loggers located on the Darwin Accelerated Stability Chamber. The temperature is set to 40°C + 2°C and 75% Relative Humidity + 5% Relative Humidity. There was one significant deviation from the set values for humidity which was investigated under BDI16-52.

6. INVESTIGATIONS:

- 6.1. **BLI16-10** was initiated for OOS moisture analysis of UR2200-006-0216-PV T=3. The OOS was determined to be an isolated incident where the T=3 sample was not properly sealed before being put into the accelerated stability chamber.
- 6.2. **BLI16-11** was initiated for OOS conductivity analysis of UR2200-006-0216-PV T=4, UR2200-007-0216-PV T=4, and UR2200-008-0216-PV T=4. It was found that the pails were being opened inside of the accelerated stability chamber thus subjecting the samples to additional moisture. New stability samples of all four lots were entered into the accelerated stability chamber and the previous stability samples were removed. These new samples were packaged into pails designated for each time period containing all four lots to be pulled at one time. This would prevent opening the packaging within the stability chamber.
- 6.3. **BLI17-04** was initiated for OOS conductivity and moisture for UR2200-006-0216-PV T=5, UR2200-007-0216-PV T=5, UR2200-008-0216-PV T=5, and Loss on Drying for UR2200-009-0216-PV T=5. It was determined that the poly pail lid was defective and allowed excess moisture to enter the pail. The increase in conductivity was further investigated in BDI17-19.
- 6.4. **BLI17-07** was initiated for following the incorrect procedure while performing conductivity analysis in BLI17-04. The OOS conductivity was not confirmed for UR2200-009-0216-PV T=5.
- 6.5. **BLI17-10** was initiated for OOS conductivity and moisture for UR2200-006-0216-PV T=6, UR2200-007-0216-PV T=6, UR2200-008-0216-PV T=6, and UR2200-009-0216-PV T=6. It was concluded that there is a direct correlation between faulty or missing gaskets and high moisture content. The increase in conductivity was further investigated in BDI17-19.

- 6.6. **BDI16-52** was initiated to investigate the low humidity noted on 10/03/16. The sample pull dates were adjusted by seven days to allow additional time in the Stability chamber upon reaching proper humidity.
- 6.7. **BDI17-19** was initiated to investigate the increase in conductivity at T=5 and T=6. It was determined that the OOS data for conductivity, moisture and loss on drying can be attributed to missing or compromised lid gaskets. Supplier Corrective Action Requests, SCR17-04 and SCR17-07, were issued to the manufacturer of the poly pails. In addition, the stability chamber exceeded the allowable humidity criteria on multiple occasions. These excursions will be evaluated by QA upon the end of Quarter One. Additionally, the storage conditions for the accelerated stability chamber are outside of the USP requirements for packaging and storage. Therefore, the product is likely to degrade and experience increases in conductivity and biuret.

7. LOT EVALUATION:

TABLE 1: PLACED ON STABILITY 03/2016

Lot	Testing Interval	Conductivity	Moisture	Melting Range	
		30 μ S max	0.5% max.	132-135°C	
UR2200-006-0216-PV	0	8.725	0.08	133.5	134.4
	1	18.61	0.1	133.6	134.9
	2	13.44	0.22	133.2	134.1
	3	28.9	0.08	133.4	134.4
	4	42.18	0.36	133	134.1
UR2200-007-0216-PV	0	9.876	0.08	133.3	134.3
	1	17.31	0.06	133.7	134.9
	2	18.38	0.1	133.3	134.3
	3	28.1	0.08	133.2	134.3
	4	39.13	0.1	133	134
UR2200-008-0216-PV	0	8.065	0.06	133.4	134.4
	1	14.1	0.04	133.6	134.8
	2	13.31	0.3	133.4	134.4
	3	20.7	0.12	133.1	134.4
	4	30.62	0.34	132.8	133.8
UR2200-009-0216-PV	0	9.251	0.06	133.6	134.7
	1	13.78	0.06	133.8	135
	2	14.5	0.1	133.3	134.3
	3	17.6	0.08	133.2	134.4
	4	26.26	0.26	133	134.1

TABLE 2: PLACED ON STABILITY 08/2016

Lot	Testing Interval	Conductivity	Moisture	Melting Range		Loss on Drying
		30 μ S max	0.5% max.	132-135°C		1.0% max.
UR2200-006-0216-PV	0	21.20	0.120	133.3	134.2	
	1	21.40	0.200	132.9	134.2	0.3082
	2	26.00	0.100	133.6	134.9	0.2489
	3	18.70	0.280	133.7	134.8	0.3190
	4	21.90	0.140	134.1	134.9	0.1938
	5	48.46	0.800	133.3	134.4	0.0908
	6	43.00	0.460	133.7	134.6	0.5868
UR2200-007-0216-PV	0	18.90	0.320	133.1	134.0	
	1	18.00	0.060	133.0	134.1	0.1529
	2	28.50	0.060	133.6	134.7	0.1385
	3	15.40	0.120	133.7	134.9	0.2578
	4	20.80	0.060	133.4	134.4	0.2176
	5	53.92	0.760	133.7	134.8	0.1267
	6	49.80	0.500	133.6	134.7	0.5454
UR2200-008-0216-PV	0	15.60	0.140	133.3	134.2	
	1	17.50	0.180	133.1	134.4	0.2200
	2	22.80	0.100	133.3	134.8	0.2515
	3	11.90	0.140	133.7	134.8	0.3310
	4	13.20	0.060	134.1	134.9	0.1719
	5	43.20	0.520	133.3	134.5	0.0879
	6	42.30	0.640	133.5	134.6	0.6323
UR2200-009-0216-PV	0	20.40	0.080	133.1	134.2	
	1	16.50	0.100	133.0	134.2	0.2790
	2	20.40	0.120	133.5	135.00	0.2988
	3	15.70	0.200	133.7	134.8	0.2311
	4	10.70	0.060	134.1	134.8	0.1451
	5	46.92	1.140	133.0	134.7	1.2213
	6	41.60	0.780	133.6	134.7	0.8870

TABLE 3: PLACED ON STABILITY 08/2017

Lot	Testing Interval	Conductivity	Moisture	Melting Range		Loss on Drying	Assay
		30 μ S max	0.5% max.	132-135		1.0% max.	98.0-102.0%
UR2200-006-0216-PV	0	13.00	0.040	133.1	134.2	0.0862	98.24
	1	23.90	0.140	133.5	134.8		98.83
	2	20.20	0.040	133.3	134.6	0.1124	99.71
	3	25.10	0.060	133.7	135.0	0.0977	98.92
	4	25.40	0.060	133.6	134.9	0.0511	99.98
	5	29.15	0.100	133.8	135.0	0.1251	99.39
	6	65.90	1.780	133.8	135.0	2.4050	101.67
UR2200-008-0216-PV	0	12.50	0.060	133.3	134.3	0.1241	98.56
	1	21.60	0.160	133.2	134.6		100.99
	2	20.60	0.040	133.3	134.6	0.0594	99.47
	3	22.60	0.060	133.4	134.9	0.0461	98.28
	4	24.10	0.060	133.8	134.8	0.0416	100.82
	5	27.98	0.100	133.8	135.0	0.2048	100.11
	6	59.40	1.580	133.6	135.0	1.9587	100.24
UR2200-009-0216-PV	0	12.00	0.160	133.2	134.6	0.1890	99.4
	1	20.80	0.160	133.2	134.6		100.41
	2	21.10	0.040	133.4	134.6	0.0907	99.9
	3	20.70	0.040	133.6	135.0	0.0275	98.22
	4	20.60	0.080	133.7	134.8	0.0384	101.49
	5	22.34	0.080	133.7	134.9	0.1599	100.02
	6	59.50	1.860	133.6	134.9	1.9360	99.59

8. CONCLUSION:

The OOS data points at T=5 and T=6 for Moisture, Conductivity and Loss on Drying can be attributed to the storage conditions of high moisture and heat above 30°C, which subjects the material to degradation. In addition, BLI17-04, BLI17-07 and BLI17-10 were initiated to investigate the OOS data. Additionally, it was determined that the round screw top poly pails had faulty and missing gaskets. There was a direct correlation between the faulty or missing gaskets and high moisture content.

In conclusion the accelerated conditions proved that the USP storage requirements are intended as the most suitable conditions for the product to meet quality criteria. USP requirements for packaging and storage are, "Preserve in well-closed containers. Store at 25°C, excursions permitted between 15°C and 30°C." The accelerated stability data from the studies in this report are disqualified since the storage conditions are deemed unsuitable as per USP which is evident in the results. The extrapolation of the data for acceleration is not valid; a viable shelf life can only be created from results of long-term stability studies for Urea. The long-term study of 24 months demonstrates a 24-month retest is viable.

9. STATEMENT OF COMMITMENT:

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

- 9.1.1. All ongoing stability data points obtained from this program will be submitted to the DMF on an annual basis.
- 9.1.2. 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.
- 9.1.3. 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.
- 9.1.4. 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.
- 9.1.5. In the event that any out of specification results are confirmed, all authorized users of the material will be notified.