BIOSPECTRA
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DEGRADATION AND IMPURITY PROFILE REPORT: UREA 6M SOLUTION

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1. PURPOSE AND SCOPE:

1.1. The impurity profiling of Urea 6M solution was intended to identify and possibly quantify impurities found in the product manufactured and purified at BioSpectra in the Bangor, Pa facility.

1.1.1. In the case where an impurity was detected, a limit was set to the maximum allowable without measurable compromise to predetermined critical quality attributes or toxicity. In the case where a limit could not be set, a procedure was written and followed to identify if the possible impurity was present or not. (i.e. an identity test, which is qualitative and not quantitative.)

1.1.2. The stages of the Urea 6M solution process that were tested are the Raw Materials, In-Process and the Finished Good.

1.1.3. One sample from each stage was used for analysis and a table was generated to include all sample results in the Degradation and Impurity Profile Report. This was performed on the first validation batch.

1.1.4. The profiling results and data allowed BioSpectra to monitor the purity and characteristics of the material through the stages of manufacturing.

1.1.5. The tests that were used to determine the presence of impurities and degradation products were as follows:

1.1.5.1. Appearance

1.1.5.1.1. Urea Raw Material

1.1.5.1.2. Urea In-Process Pre-filtration

1.1.5.1.3. Urea 6M Finished Good Beginning Tote

1.1.5.2. % w/w Assay

1.1.5.2.1. Urea Raw Material

1.1.5.2.2. Urea In-Process Pre-filtration

1.1.5.2.3. Urea 6M Finished Good Beginning Tote

1.1.5.3. Identification (IR)

1.1.5.3.1. Urea Raw Material

1.1.5.3.2. Urea In-Process Pre-filtration

1.1.5.3.3. Urea 6M Finished Good Beginning Tote

1.1.5.4. Organic Impurities:

1.1.5.4.1. Urea Raw Material

1.1.5.4.2. Urea In-Process Pre-filtration

1.1.5.4.3. Urea 6M Finished Good Beginning Tote

1.1.5.5. Elemental Impurities USP <232><233> with the addition of Iron

1.1.5.5.1. Urea Raw Material

1.1.5.5.2. Urea In-Process Pre-filtration

1.1.5.5.3. Urea 6M Finished Good Beginning Tote

1.1.5.6. Molarity

1.1.5.6.1. Urea In-Process Pre-filtration

1.1.5.6.2. Urea 6M Finished Good Beginning Tote

1.1.5.7. pH @ 25°C

1.1.5.7.1. Urea Raw Material

1.1.5.7.2. Urea In-Process Pre-filtration

1.1.5.7.3. Urea 6M Finished Good Beginning Tote

1.1.5.8. Residual Solvents: 2-Propanol

1.1.5.8.1. Urea Raw Material

1.1.5.8.2. Urea In-Process Pre-filtration

1.1.5.8.3. Urea 6M Finished Good Beginning Tote

1.2. Routine USP/EP Water for Injection testing was documented in the report for the week the batch was manufactured. If a water tote(s) was used to manufacture the batch, the Routine USP/EP Water for injection testing was documented for the week the tote is filled for use, as Water for Injection is an approved Raw material for this process.

1.3. All results were recorded in the appropriate laboratory documentation. The results are detailed and analyzed in a formal report. This report includes all relevant data, as well as references to the initial documented results. This report discusses any impurities found in the product and includes specification for any limits on the impurities found, where applicable.

2. RESPONSIBILITIES:

2.1. The Executive Director of Quality Control or designee was responsible for control, implementation, training and maintenance of this procedure.

2.2. The QC Analysts were responsible for performing the testing stated in the protocol.

2.3. The QC Compliance Team was responsible for creating and approving the Degradation and Impurity Profile Report.

3. REFERENCES:

3.1. BSI-ATM-0006, Urea Testing Methods

3.2. BSI-ATM-0037, USP/EP Water for Injection Testing Methods

3.3. BSI-ATM-0073, Analytical Method of Analysis: Guanidine Thiocyanate, MOPS and Urea via ICP-MS

3.4. BSI-PRL-0357, Analytical Method Verification Protocol: Urea UPLC Assay

3.5. BSI-PRL-0358, Analytical Method Verification Protocol: Urea UPLC Organic Impurities

3.6. BSI-PRL-0465, Degradation and Impurity Profile Protocol: Urea 6M Solution

3.7. BSI-RPT-1052, Elemental Impurity Assessment: Urea 6M 2021-2022

3.8. BSI-SOP-0098, Balance SOP

3.9. BSI-SOP-0102, Degradation and Impurity Profiling SOP

3.10. BSI-SOP-0126, Laboratory Notebooks

3.11. BSI-SOP-0303, NexION 350X ICP-MS SOP

3.12. Current EP

3.13. Current USP

3.14. ICH Q3D Guideline for Elemental Impurities

4. PROCEDURE:

4.1. APPEARANCE:

4.1.1. Refer to the Degradation and Impurity Profile Protocol: Urea 6M Solution for testing methods and requirements. The results of the Appearance analysis are detailed in the table below.

TABLE 1: APPEARANCE

Lot Number	Stage	Specification	Result
UREA-0221-00011	Raw Material	Report	White Crystalline Powder
UREA-0121-00041-PV Time: 1410	In-Process		Colorless Liquid
UREA-0121-00041-PV Beginning	Finished Good	Colorless Liquid	Colorless Liquid

4.2. ASSAY/IMPURITIES:

4.2.1. Refer to the Degradation and Impurity Profile Protocol: Urea 6M Solution for testing methods and requirements. The results of the Assay/Impurities analysis are detailed in the tables below.

TABLE 2: ASSAY

Lot Number	Stage	Specification	Result
UREA-0221-00011	Raw Material	98.0-102%	98.7%
UREA-0121-00041-PV Time: 1410	In-Process	Report	32.9%
UREA-0121-00041-PV Beginning	Finished Good		32.65371%

TABLE 3: IMPURITIES

Lot Number	Stage	Specification	Result
UREA-0221-00011	Raw Material	RCA: NMT 0.1% Unspecified: NMT 0.1% Total: NMT 2.0%	RCA: <0.1% Unspecified: <0.1% Total: <2.0%
UREA-0121-00041-PV Time: 1410	In-Process	Report for RCA, Unspecified and Total	RCA: <0.05% Unspecified: ND Total: <0.05%
UREA-0121-00041-PV Beginning	Finished Good		RCA: <0.05% Unspecified: ND Total: <0.05%

4.3. IDENTIFICATION (IR):

4.3.1. Refer to the Degradation and Impurity Profile Protocol: Urea 6M Solution for testing methods and requirements. The results of the Identification (IR) analysis are detailed in the table below.

TABLE 4: IDENTIFICATION (IR)

Lot Number	Stage	Specification	Result
UREA-0221-00011	Raw Material	Conforms to Standard	Passes Test; 0.996139
UREA-0121-00041-PV Time: 1410	In-Process		Passes Test; 0.985375
UREA-0121-00041-PV Beginning	Finished Good		Conforms to Standard; 0.992763

4.4. ELEMENTAL IMPURITIES, OPTION 1:

4.4.1. Refer to the Degradation and Impurity Profile Protocol: Urea 6M Solution for testing methods and requirements. The results of the Identification (IR) analysis are detailed in the table below.

TABLE 5: ELEMENTAL IMPURITIES

Lot Number	Stage	Specification	Result
UREA-0221-00011	Raw Material	Meets USP <232><233> Option 1	Refer to BSI-RPT-1052 for Elemental Impurity Assessment
UREA-0121-00041-PV Time: 1410	In-Process		
UREA-0121-00041-PV Beginning	Finished Good		

4.5. **MOLARITY:**

4.5.1. Refer to the Degradation and Impurity Profile Protocol: Urea 6M Solution for testing methods and requirements. The results of the Molarity analysis are detailed in the table below.

TABLE 6: MOLARITY

Lot Number	Stage	Specification	Result
UREA-0121-00041-PV Time: 1410	In-Process	5.8-6.2M	6.0M
UREA-0121-00041-PV Beginning	Finished Good		5.9M

4.6. **pH @ 25°C:**

4.6.1. Refer to the Degradation and Impurity Profile Protocol: Urea 6M Solution for testing methods and requirements. The results of the pH @ 25°C are detailed in the table below.

TABLE 7: pH @ 25°C

Lot Number	Stage	Specification	Result
UREA-0221-00011	Raw Material	Monitor	7.07 @ 25.4°C
UREA-0121-00041-PV Time: 1410	In-Process	7-10 @ 25°C ± 2°C	9 @ 23.1°C
UREA-0121-00041-PV Beginning	Finished Good		8 @ 23.1°C

4.7. **RESIDUAL SOLVENTS:**

4.7.1. Refer to the Degradation and Impurity Profile Protocol: Urea 6M Solution for testing methods and requirements. The results of the Residual Solvents testing are detailed in the table below.

TABLE 8: RESIDUAL SOLVENTS

Lot Number	Stage	Specification	Result
UREA-0221-00011	Raw Material	Report for 2-Propanol	None Detected
UREA-0121-00041-PV Time: 1410	In-Process		None Detected
UREA-0121-00041-PV Beginning	Finished Good		None Detected

5. CONCLUSION:

5.1. All samples met the specifications for the required analyses as dictated in the Degradation and Impurity Profile Protocol: Urea 6M Solution.

5.2. The reviewed USP/EP Water for Injection testing from the week the batch was manufactured (12/13/21) has been added as supporting documents to this report.

5.3. It can be concluded that there are no additional identifiable impurities present in the Urea 6M Solution material at any stage of the process at this time.