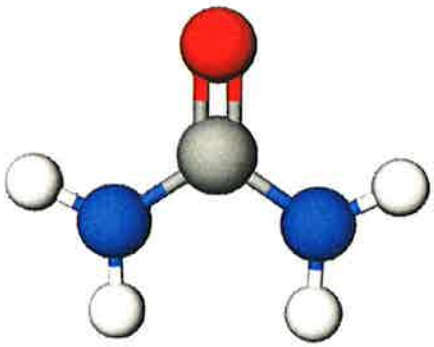
BIOSPECTRA
Premium Pharmaceutical Ingredients
100 Majestic Way, Bangor, PA 18013 / www.biospectra.us

# UREA



# BIO ACTIVE GRADE REGULATORY PACKET

**Signature/Date:** Cassie Baun 6/23/20

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# SECTION 1 - UREA BIO ACTIVE GRADE

## 1.1 General Product Information

1.1.1 Product Name:

Urea

1.1.2 Product Code:

UR2220

1.1.3 Scope:

This regulatory packet will provide the quality and regulatory information regarding the manufacturing, testing, packaging, storage, release, shipping and handling of Bio Active Grade Urea manufactured by and at the BioSpectra, Bangor, PA facility.

1.1.4 Molecular Formula:

$NH_2CONH_2$

1.1.5 Molecular Weight:

60.06 g/mol.

## 1.2 Manufacturing, Packaging, Release Site and Supplier Information

1.2.1 General Information:

BioSpectra manufactures Urea in its Bangor, PA facility. Urea is manufactured, packaged, stored, tested and released at BioSpectra's Bangor, PA facility.

1.2.2 Manufacturing:

The manufacturing of Urea is performed at BioSpectra's Bangor, PA facility utilizing multi-use equipment. Equipment used in the manufacturing of Urea is cleaned in accordance with BioSpectra's Process Cleaning Validation Master Plan.

1.2.3 Packaging:

The packaging and repackaging of Urea occur in the following BioSpectra site:
BioSpectra Bangor, PA Facility: 100 Majestic Way, Bangor, PA 18013

1.2.4 Testing for Release:

Testing and release of Urea may be performed at:
BioSpectra Bangor, PA Facility: 100 Majestic Way, Bangor, PA 18013
BioSpectra Stroudsburg, PA Facility: 1474 Rockdale Lane, Stroudsburg, PA 18360

1.2.5 GMP Compliance Statement:

Bio Active Grade Urea is suitable for use as a non-Sterile Active Pharmaceutical Ingredient manufactured in accordance with the ICH Q7 Good Manufacturing Practice Guide. This grade of Urea is not suitable to be used as a Sterile or Injectable Active Pharmaceutical Ingredient, Drug Product or Household Item.

## 1.3 Physico-Chemical Information

1.3.1 CAS Number:

CAS# 57-13-6

1.3.2 Origin:

The origin of Urea is through synthetic chemical manufacturing using approved raw materials, which are further purified in accordance with ICH Q7 guidelines. Only raw materials of synthetic origin are used in the synthesis and purification of Urea.

1.3.3 Synonyms:

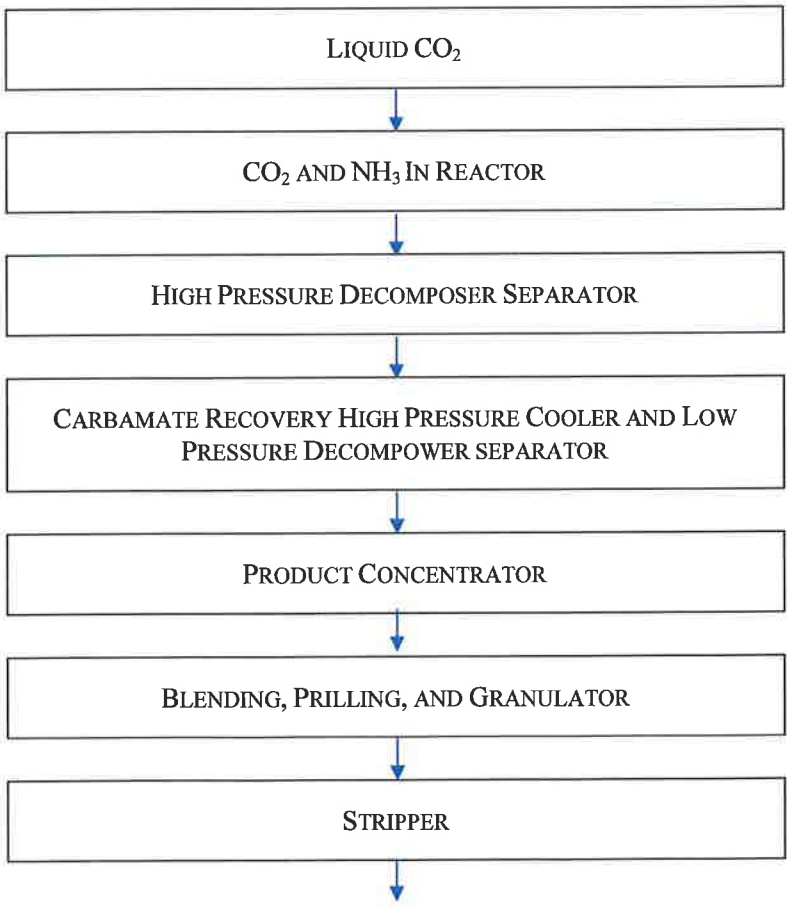
Urea
Carbamide
Carbonyldiamide

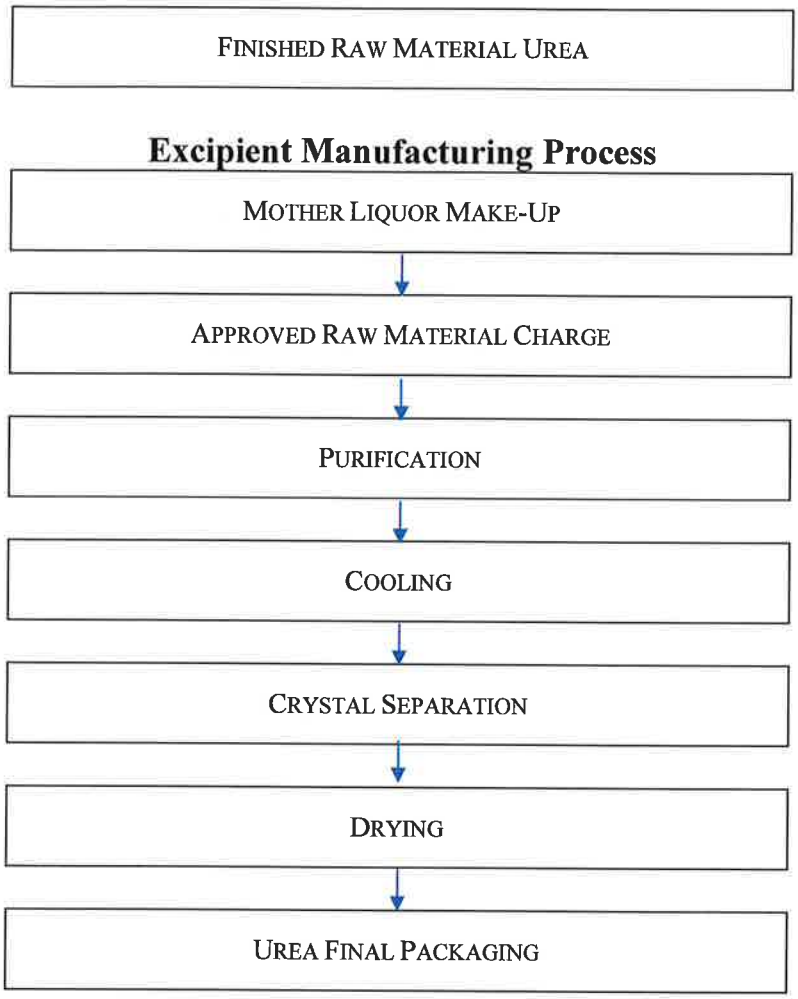
1.3.4 Morphological Form:

White Crystalline Powder

1.3.5 Manufacturing Process:

The manufacturing process for Urea, Bio Active Grade is by performed as follows:






1.3.6 Specifications:

Available upon request.

## 1.4 Regulatory Information

1.4.1 Compendial Compliance:

USP Monograph

1.4.2 Master File:

Drug Master File (DMF) is available for this grade of product.
EDQM Certificate of Suitability is currently not available for this product.

1.4.3 BSE/TSE Statement:

BioSpectra certifies that all Urea manufactured at BioSpectra is BSE/TSE free. In addition, raw materials used in the manufacturing process are certified BSE/TSE free based on approved certification received from the Raw Material supplier.

1.4.4 Allergens/Hypersensitivities:

Urea is not manufactured with or using any of the following substances: Casein, Corn, Fish, Lactose, Tartrazine, Crustaceans, Soy Protein, Vanillin, Yeast, Wheat, Celery, Nuts, Beef, Cocoa, Peanuts, Chicken, Benzoic Acid, Sesame, Shell Fish, Lupin, Glutamate, Mollusk, Gluten, Azo Dyes, Legumes, Chicken's Egg, Cinnamon, Nut Oil, Soya Oil, Coriander, Peanut Oil, Rye, Mustard, Sesame Oil, Pork, Sulfite, Barley, Oats, Milk, Kamut, Spelt, and Soybeans as stated by the Raw Material supplier.

1.4.5 GMO Information:

BioSpectra certifies that all Urea manufactured at BioSpectra and any raw materials used in the manufacture of Urea at BioSpectra are not subject to genetic modification.

1.4.6 Residual Solvents:

BioSpectra certifies that all Urea manufactured at BioSpectra complies with the requirements of the ICH Q3C Residual Solvents Guideline and USP <467> Residual Solvents. There are no Class 1, 2, 3 or other solvents used or produced in the manufacturing or purification of Urea.

1.4.7 Pallet Statement:

BioSpectra certifies that all pallets used in the packaging of Urea manufactured at BioSpectra are ISPM 15 compliant.

1.4.8 Melamine Statement:

BioSpectra certifies that based on the manufacturing process and the controlled handling, storage, and analysis of Urea and its raw materials, there is low risk for melamine contamination in the product. Additionally, when tested for melamine, this product reports less than 0.15 ppm.

## 1.5 Miscellaneous Product Information

1.5.1 Description of Batch:

The Urea process is a batch process where each batch yields approximately 200 kg.

1.5.2 Lot/batch numbering system:

The lot numbering system at BioSpectra employs the following format: 6 alphanumerical digits followed by a hyphen, 3 numerical digits followed by a hyphen, and finally 4 numerical digits. A sample lot number would appear as:

UR2220-001-0620

The first two digits are alpha digits which indicate the material manufactured, where UR represents Urea. The third digit is a numeric digit which indicates the compliance of the material where 2 represents ICH Q7 compliant Active Pharmaceutical Ingredient. The fourth digit is a numeric digit which indicates the phase of the material where 2 represents a crystal or powder. The fifth and sixth digits are two numeric digits which indicate the set of specifications for the material where 20 is reserved for the customer. The seventh, eighth and ninth digits are numeric digits representing the sequential batch manufactured. The tenth and eleventh digits are two numeric digits which represent the month of manufacture. The twelfth and thirteenth digits are two numeric digits which represent the year of manufacture.

1.5.3 Expiration date and/or recommended re-evaluation interval:

Urea Bio Active Grade material undergoes a 3-year stability testing program with at least 3 years of stability data available.

1.5.4 Storage and shipping conditions:

Ship and Store between 15°C and 30°C.
Store in a clean, dry and well-ventilated area.
Store in the original container.

1.5.5 Packaging:

Packaging information is available through the following: https://Biospectra.us/packaging

# SECTION 2 – SITE QUALITY OVERVIEW

## 2.1 Facility Overview

### 2.1.1 Scope:

Site Name: BioSpectra Bangor, PA Facility
Address: 100 Majestic Way, Bangor, PA 18013
Active Pharmaceutical Ingredient Covered by this Datasheet: Urea

### 2.1.2 Customer Audit Policy:

The Bio Active Grade Urea allows for customer audits as required by the customer. Access to the raw material supply chain is also available. Each customer audit provides a general overview of processing information and facility operations.

### 2.1.3 Site Details:

General Site Information

BioSpectra was founded in 1994 and was officially incorporated in the State of Pennsylvania in 1995. The first BioSpectra manufacturing facility was opened in Sciota, PA in March of 1996. This facility was created for the cGMP manufacturing of Biological Buffers.

BioSpectra opened the Stroudsburg, PA facility in December of 2000. Between 2000 and 2003, BioSpectra moved its processes from the Sciota, PA facility to its Stroudsburg, PA facility. This site is registered with the US Food and Drug Administration. The processes were initially validated in the Stroudsburg facility throughout 2000 and 2003 and revalidated in accordance with BioSpectra's approved Manufacturing Process Validation Master Plan. The manufacturing operations at this site operate 24 hours per day 7 days per week.

BioSpectra purchased the Bangor, PA facility in December of 2012. This facility develops new processes, conducts research and development, and manufactures Active Pharmaceutical Ingredients, Excipients, and Life Science Intermediates, as well as Custom Buffers and Blends. This site is registered with the US Food and Drug Administration. The manufacturing operations at this site operate 24 hours per day 7 days per week.

Facility Size and Composition

The BioSpectra Bangor facility is approximately 150,000 square feet in size and is comprised of various Zones. Each Zone represents a particular geographical portion of the facility. Any one zone may include multiple operational areas, which include manufacturing, packaging, storage or further processing areas. The map of the facility contains details of each zone including the materials of construction of the equipment used in each zone of the facility.

Site Activities Conducted:

The activities conducted at the BioSpectra Bangor, PA Facility include the following:

- Chemical Manufacturing
- Multi-compendial Testing
- Enzyme Analysis (If Applicable)

- Blending
- Wet Chemistry Analysis
- Spectroscopy: UV/VIS, AA, IR
- Karl Fischer Titrations
- Melting Point Determination
- Residue on Ignition
- Titrations

2.1.4 Primary applications of products produced at this site:

At the Bangor, PA site Bio Active Grade Urea is manufactured in accordance with ICH Q7 Guidance Documents and is intended to be used as an Active Pharmaceutical Ingredient for use in drug product manufacturing.

2.1.5 Facility production of antibiotics, steroids, or hormone products:

There is no production of antibiotics, steroids or hormones conducted at any BioSpectra facility.

2.1.6 Product Release:

Products manufactured by BioSpectra are tested to ensure each batch conforms to assigned specifications. Quality Control performs all analytical testing of each batch of product. Quality Assurance reviews all batch documentation for release. All packaged and prepared materials are inspected before final shipment.

2.1.7 Service Providers:

Service Providers are approved and qualified in accordance with BioSpectra's Service Provider Approval Program. This includes completion of appropriate questionnaires and verification of quality, capabilities and performance via audits and inspections.

## 2.2 Compliance Evidence

2.2.1 ISO Registration and ISO Certification:

BioSpectra Facilities are not registered with ISO.

2.2.2 General GMP Statement:

BioSpectra's quality system is called the Quality System V. This system is designed to state and define the compliance standard to which all BioSpectra operations are held. The BioSpectra Quality System V was derived from the interpretations of ICH Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients and the Joint IPEC-PQG Good Manufacturing Practice Guide for Pharmaceutical Excipients. All personnel are GMP trained on a scheduled frequency which ensures their awareness and understanding of cGMP guidelines. The facility is inspected on a scheduled frequency to verify continuous compliance in accordance with BioSpectra's Quality System V. Specific manufacturing processes conducted at BioSpectra's facilities are validated and revalidated in accordance with BioSpectra's approved Manufacturing Process Validation Master Plan. All products available from BioSpectra are available with distinct Key Compliance Attributes.

BioSpectra manufactures and processes Chemical Reagents, Life Science Intermediates, Excipients and Active Pharmaceutical Ingredients. The manufacturing of BioSpectra products includes a validation of the processes, qualification of the utilities and equipment and identifying compliance attributes according to the regulatory needs of the product or process. BioSpectra also

performs various other processing or handling of products. This includes blending, particle manipulation, custom solutions or packaging.

2.2.3 Other certifications or external audit programs:

BioSpectra has been audited by third party auditors in support of supply chain management. Further information is available through BioSpectra's Regulatory Department.

## 2.3 ICH Q7 GMP Compliance Details

BioSpectra manufactures Bio Active grade products in accordance with ICH Q7 Guidance Documents.

2.3.1 Quality Management Systems-Active Pharmaceutical Ingredient Quality Systems:

General Requirements

- BioSpectra has created and implemented the Quality System V, which provides the necessary requirements for all aspects in the manufacture, testing and release of all BioSpectra products.
- Senior Management Review is conducted quarterly to review all investigations, internal and external audits, as well as corrective actions and preventative actions.
- BioSpectra's quality policies ensure that all operations conducted at BioSpectra are performed in accordance with ICH Q7 guidelines.
- All responsibilities of the Quality Unit are clearly defined.
- Bio Active Grade products are manufactured in accordance with BioSpectra's Manufacturing Process Validation Master Plan. All utilities, equipment and processes are qualified for use in the processing of a Bio Active Product.

Documentation Requirements

- Documentation rules and standards are defined by BioSpectra's Document Creation and Revision Plan, as well as the Record Storage, Retention and Control Procedures. Documentation entry requirements and rules are defined in the Documentation Entry and Error Correction Procedure.

Change Control

- BioSpectra's Change Control system is defined by the Change Control SOP. Any changes are detailed in the Change Control Program and must be approved by Quality, Management, and any department responsible for the change. Customer notification of any changes are provided in the mutually agreed upon timeframe as required.

2.3.2 Management Responsibility:

- Management of BioSpectra reviews operations on a daily basis.
- Management reviews and assesses the adequacy and efficiency of the Quality System. This is conducted through Senior Management reviews, which review CAPAs, Customer Complaints, Discrepancies, Lab Investigations, Internal Audits, External Audits and Batch Failures.
- Management provides necessary objectives for appropriate planning of operations, for continuous development and growth.

2.3.3 Resource Management:

Provision of Resources

- Management develops and assigns the necessary resources to ensure all operations at BioSpectra are performed efficiently.

Human Resources

- Each employee engaged in the manufacturing, processing, packing, testing or holding of a BioSpectra product has the education, training and experience, or any combination thereof, to enable that person to perform his or her assigned functions. BioSpectra provides training to all employees in the particular operations specific to that employee's job description, BioSpectra's Safety Program and cGMPs. Qualified Individuals perform cGMP training on a continual basis and with sufficient frequency to ensure that each BioSpectra employee remains familiar with cGMPs. BioSpectra is a non-union facility.

Infrastructure (Facilities and Equipment)

- Facility utilities and equipment are qualified to perform as intended and are maintained in accordance with BioSpectra's Preventative Maintenance Program.

Work Environment

- In order to protect the operator, visitor and the product, BioSpectra requires hairnets, beard nets (where applicable), uniforms, safety glasses or goggles, disposable laboratory coats and/or sleeves (where applicable) and safety shoes to be worn in all manufacturing areas. (Visitors may be exempt from the requirement of safety shoes). Production area cleaning is performed and documented at the conclusion of each batch. Periodic cleaning of a process is performed, verified, and documented every 10 manufactured batches. The samples must meet designated rinse requirements to ensure that all equipment used in the manufacture of BioSpectra products remains free of contamination and to ensure production of the purest product is available.

2.3.4 Product Realization:

Design and Development

- All processes at BioSpectra are developed, qualified and validated for intended use. Multi-use equipment is cleaned in accordance with BioSpectra's approved Process Cleaning Validation Master Plan.

Purchasing

- BioSpectra purchases all controlled items only from BioSpectra's Approved Supplier List.

Production and Service Provision

- The manufacturing of BioSpectra products includes a validation of the processes, qualification of the utilities and equipment and identifying compliance attributes according to the regulatory needs of the product or process.

Control of Measuring and Monitoring Devices

- BioSpectra has an extensive Calibration and Preventative Maintenance Program for the equipment and measuring devices utilized in manufacturing as well as the Quality

Control Laboratory. All QC test methods are validated or verified according to ICH, USP <1225> and USP <1226> guidelines.

2.3.5 Measurement, Analysis and Improvement:

General

- BioSpectra provides complete testing of Bio Active Grade products in each phase of manufacturing from raw materials to finished goods. The Stability Testing Program and Impurity Profiles are also maintained for each product. The QC Laboratory has Multi-Compendial testing capabilities and uses state-of-the-art calibrated equipment to ensure accurate testing. All testing is reviewed by QC and verified by QA during Certificate of Analysis issuance. All and batch records are reviewed by the Quality Assurance department before release and shipment of product.

Monitoring and Measurements

- BioSpectra handles all customer complaints in accordance with the BioSpectra Written and Verbal Complaint procedure. Customer Complaints are evaluated for each product annually as a part of the Annual Product Review and reported to Senior Management quarterly.
- BioSpectra conducts Internal Audits in accordance with the Internal Audit SOP. Internal Auditors may not audit areas of their own work.
- Critical Process Parameters, Critical Quality Attributes, OOS and Process Deviations are evaluated during the Annual Product Reviews.
- Analytical Methods used for Urea analysis are validated or verified in accordance with USP <1225> and <1226> and other regulatory guidance.
- All data for testing is recorded directly into permanently bound, sequentially numbered laboratory notebooks or data cards using permanent ink. All sample identification information is recorded on sample labels, as well as in the laboratory notebooks or data cards.
- All electronic printouts of raw data are retained by BioSpectra for a minimum of five years.
- Each analysis performed is signed and dated by the Analyst performing the analysis.
- There are detailed Laboratory procedures regarding the execution of analytical methods and the preparation of solutions.
- USP Primary Reference Standards may be used when available.
- Finished Good Testing for Bio Active Grade material is performed on every lot of finished product manufactured prior to release. Testing is reviewed by Quality Control or a qualified designee and verified by Quality Assurance prior to the release of material.
- OOS results are documented and investigated. All re-tests and re-samples must be justified prior to execution.
- All Raw Material and Finished Good Samples are retained for five years. Initially, approximately three hundred grams of sample is retained, which is enough to complete Finished Good analysis twice.
- Impurity and Degradation Profiles are completed on the product during validation and during each subsequent validation.
- Stability of Urea is determined in Accordance with ICH Q1A.

Control of Nonconforming Product

- Materials that do not conform to specifications are isolated in quarantine and an OOS investigation as well as a deviation investigation, as applicable, is performed to determine the root cause of the nonconformance. Material is completely tested prior to shipment and shipments are not released by Quality until all investigations are concluded with a final disposition statement of the product.
- Material may be reprocessed one time, where applicable, as this is included as part of the process validation.
- Additional reworking may be conducted after a risk analysis is completed and Temporary Operating Instructions are issued. TOI must be approved by QA, QC and Production. Any material that is reworked must be placed into the BioSpectra Stability Program.
- Active Pharmaceutical Ingredients that are returned to BioSpectra are evaluated by Quality for any risk to the production process and if the material is deemed acceptable it is tested and used as raw material.

Analysis of Data

- All Critical Quality Attributes and measurable Critical Process Parameters are evaluated statistically during the Annual Product Review. Results and trends of the Annual Product Review are reported to Senior Management annually.

Improvement

- OOS and Deviation Investigations, Internal and External Audit Reports and Customer Complaints are reviewed during the Annual Product Reviews in addition to the Senior Management Reviews. CAPAs are presented at the conclusion of the investigation reports and the audit responses.

# SECTION 3 – SITE AND SUPPLY CHAIN SECURITY OVERVIEW

## 3.1 Scope

3.1.1 BioSpectra Bangor, PA Facility: 100 Majestic Way, Bangor, PA 18013

3.1.2 Urea is the only Active Pharmaceutical Ingredient covered by this Regulatory Datasheet.

## 3.2 Supply Chain Security

3.2.1 Evaluation of Carriers

- All non-BioSpectra-owned carriers utilized by BioSpectra are approved through mutual agreement with customers or as requested by the customer.

3.2.2 Tamper Evident Packaging

- BioSpectra packaging may be sealed using an approved sequentially numbered and traced BioSpectra seal. The seals provide evidence of tampering.
- Seals may be issued by the Director of Manufacturing or trained designee and traceability of each seal may be evident with a seal accountability form as well as the sequential numbering.
- Tamper Evidence may be apparent using the BioSpectra sequentially numbered seals.

3.2.3 Environmental Controls are not applicable for the supply chain security of Urea in its current container closure system.

3.2.4 Qualification of Distributors is performed as necessary based on customer requests and expectations.

3.2.5 Qualification of forwarders/brokers is not applicable for Urea.

3.2.6 Qualification of intermediate storage locations is not applicable for Urea.

3.2.7 Repacking and relabeling activities are not applicable for Urea once it is shipped from a BioSpectra facility.

## 3.3 Safety and Environmental Information

3.3.1 BioSpectra's Health and Safety Program is comprised of a number of controlled policies aimed at protecting employees, the surrounding community, the environment, and the customers BioSpectra serves. These policies have been developed using regulatory guidelines and industry regulations.

3.3.2 BioSpectra is not currently registered to ISO 14001, OHSAS 18001, or Responsible Care.

3.3.3 BioSpectra has created an Emergency Action Plan to provide all BioSpectra employees with the appropriate procedure to safely and effectively respond to or safely evacuate from an emergency situation at either BioSpectra facility. This plan provides information for the appropriate response to be used in the event of a fire, medical, chemical spill/release, security threat or weather-related emergency.

# SECTION 4 – CONTACT INFORMATION

https://www.biospectra.us/about-us/commercial-marketing-team