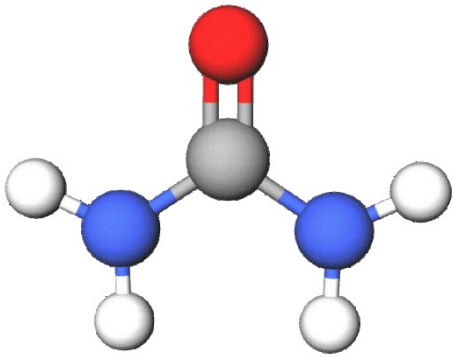
BIOSPECTRA

Urea
Regulatory Packet



BIO PHARMA GRADE

BIOSPECTRA

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Section 1 – General Product Information

1.1 Product Name:

Urea

1.2 Product Code:

UR4XXX

1.3 Scope:

This regulatory packet will provide the quality and regulatory information regarding the manufacturing, packaging, storage, release, shipping and handling of Bio Pharma Grade Urea UR4XXX manufactured by and at BioSpectra's, Stroudsburg, PA facility.

1.4 Molecular Formula:

NH_2CONH_2

1.5 Molecular Weight:

60.06 g/mol.

Section 2 – Manufacturing, Packaging, Release Site and Supplier Information

2.1 General Information:

BioSpectra manufactures Urea UR4XXX in its Stroudsburg, PA facility. Urea may be packaged, stored and tested and released at BioSpectra's Stroudsburg, PA facility.

2.2 Manufacturing:

The Manufacturing of Urea UR4XXX is performed at BioSpectra's Stroudsburg, PA facility and is conducted in a dedicated processing area using only dedicated equipment.

2.3 Packaging:

The packaging of Urea UR4XXX occurs in the following BioSpectra sites:
BioSpectra, Stroudsburg PA Facility: 1474 Rockdale Lane, Stroudsburg PA 18360
BioSpectra, Bangor PA Facility: 100 Majestic Way, Bangor PA 18013

2.4 Testing for Release:

The BioSpectra site for testing and release of Urea UR4XXX is:
BioSpectra, Stroudsburg PA Facility: 1474 Rockdale Lane, Stroudsburg PA 18360
BioSpectra, Bangor PA Facility: 100 Majestic Way, Bangor PA 18013

2.5 GMP Compliance Statement:

Bio Pharma Grade Urea UR4XXX is manufactured in accordance with cGMP guidelines and is suitable to be used only as the following: IPEC Compliant GMP Manufactured Chemical, for use in further Manufacturing or as a Reagent for Laboratory and Research. This Grade of Urea is not suitable to be used as an Active Pharmaceutical Ingredient, Drug, Drug Product or Household Item.

Section 3 – Physico-chemical Information

3.1 CAS Number:

Urea CAS 57-13-6

3.2 Origin:

The origin of Urea is through synthetic chemical manufacturing using approved raw materials, which are further purified in accordance with cGMP guidelines. Only raw materials of synthetic origin are used in the synthesis of Urea UR4XXX.

3.3 Synonyms:

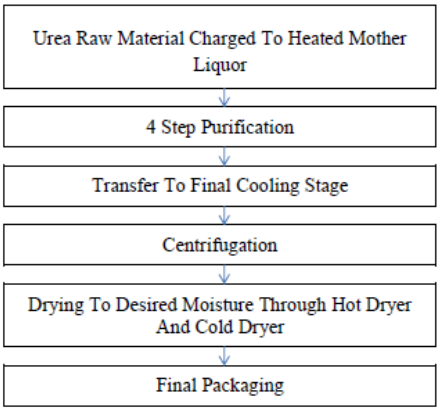
Urea
Carbamide
Carbonyldiamide

3.4 Morphological Form:

White Crystalline Powder

3.5 Manufacturing Process:

The Urea UR4XXX manufacturing process is by performed by the following:



3.6 Specifications:

See attached specification sheet.

Section 4 – Regulatory Information

4.1 Compendial Compliance:

Not Applicable

4.2 Master File:

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

4.3 BSE/TSE Statement and Viral safety:

BioSpectra certifies that all Urea UR4XXX manufactured at BioSpectra is BSE/TSE free. In addition, all raw materials used in the process are certified BSE/TSE free.

4.4 Allergens/Hypersensitivities:

There are no known major food allergens (as defined by FDA and WHO) in the manufacture of this product.

4.5 GMO Information:

BioSpectra certifies that all Urea UR4XXX manufactured at BioSpectra and its raw materials are not derived from or come in contact with animal parts, products, and/or byproducts. In addition, Urea manufactured at BioSpectra and any raw materials used in the manufacture of Urea at BioSpectra are not subject to genetic modification.

4.6 Residual Solvents:

BioSpectra certifies that all Urea UR4XXX 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.

4.7 Metal Catalyst and Metal Reagent Residues:

Urea Manufactured by BioSpectra is manufactured without the use of metal catalysts and metal reagents. There are no known risks to metal residues in this product.

4.8 Kosher/Halal status:

No Status

Section 5 – Miscellaneous Product Information

5.1 Description of Batch:

The Urea UR4XXX process is a continuous manufacturing process where each batch is validated to yields 1kg up to approximately 24,000kg.

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:

UR4XXX-001-0919

The first two digits are alpha digits which indicate the material manufactured, UR represents Urea. The third digit is a numeric digit which indicates the compliance of the material where 4 represents IPEC compliant Chemical, the fourth digit is a numeric digit which indicates the phase of the material where X represents the phase, the fifth and sixth digits are two numeric digits which indicate the set of specifications for the material where XX 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.

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

The recommended retest period for Urea is two years from the date of manufacture.

5.4 Storage and shipping conditions:

Ship and Store between 15°C and 30°C.
Store in clean and dry area
Store in the original container

5.5 Packaging:

100 gram bottle
Package: 8 ounce, White HDPE UN Square, Leak proof bottle
Cap: 45mm PP Tamper Evident Blue screw cap
Dimensions of bottle and cap:
Outside Height: 5.25 ± 0.5 inches
Outside Width: 2.25 ± 0.5 inches
Label: BioSpectra approved white matte paper
Shipping: Outer box- cardboard

500 gram bottle
Package: 33 ounce, White HDPE UN Square, Leak proof bottle
Cap: 54mm PP Tamper evident Blue screw cap
Dimensions of bottle and cap:
Outside Height: 9.0 ± 0.5 inches
Outside Width: 3.25 ± 0.5 inches
Label: BioSpectra approved white matte paper
Shipping: Outer box- cardboard

1 kilogram bottle
Package: 50 ounce, White HDPE UN Square, Leak Proof bottle
Cap: 80mm PP Tamper evident Blue screw cap
Dimensions of bottle and cap:
Outside Height: 8.5 ± 0.5 inches
Outside Width: 4.0 ± 0.5 inches
Label: BioSpectra approved white matte paper
Shipping: Outer box- cardboard

10 kilogram pail
Package: 10 kilograms of material in 5.0 gallon, White HDPE UN Round pail with liner
Lid: blue tamper evident lid with neoprene gasket
Dimensions of pail and lid:
Outside Height: 16.0 ± 0.5 inches
Outside Bottom Diameter: 10.25 ± 0.5 inches
Label: BioSpectra approved white matte paper
Shipping: Outer box- cardboard if shipped parcel
Palletized 42" x 48", 4 way, flush, heat treated pallet with 42" x 48", cardboard pallet liner and stretch wrapped in shrink wrap

25 kilogram pail
Package: 25 kilograms of material in 12 gallon, White HDPE UN Round pail with liner
Lid: blue tamper evident lid with neoprene gasket
Dimensions of pail and lid:
Outside Height: 21.5 ± 0.5 inches
Outside Bottom Diameter: 13.0 ± 0.5 inches
Label: BioSpectra approved white matte paper
Shipping: Outer box- cardboard if shipped parcel
Palletized 42" x 48", 4 way, flush, heat treated pallet with 42" x 48", cardboard pallet liner and stretch wrapped in clear shrink wrap

20 Gallon Poly drum
Package: 85 pounds of material in 20 gallon Poly Drum with liner
Lid: Round Poly lid with snap on gusset and metal level lock
Dimensions of pail and lid:
Outside Height: 30.5 ± 0.5 inches
Outside Bottom Diameter: 15.9 ± 0.5 inches
Label: BioSpectra approved white matte paper
Shipping: Outer box- cardboard if shipped parcel
Palletized 42" x 48", 4 way, flush, heat treated pallet with 42" x 48", cardboard pallet liner and stretch wrapped in clear shrink wrap

26 Gallon Fiber drum
Package: 50 kilograms of material in 26 gallon, Fiber Drum with liner
Lid: Brown fiberboard with galvanized steel Chime and Lock Ring
Dimensions of pail and lid:
Outside Height: 33± 0.5 inches
Outside Bottom Diameter: 16± 0.5 inches
Label: BioSpectra approved white matte paper
Shipping: Outer box- cardboard if shipped parcel
Palletized 42” x 48”, 4 way, flush, heat treated pallet with 42” x 48”, cardboard pallet liner and stretch wrapped in clear shrink wrap

Packaging weight tolerances can range from 0.10g to 0.5kg depending on the package size and scale used.

SITE QUALITY OVERVIEW

Section 1 – Facility Overview

1.1 Scope:

Site Name: BioSpectra Stroudsburg, PA Facility
Address: 1474 Rockdale Lane, Stroudsburg PA, 18360
Chemical Covered by this Datasheet: Urea UR4XXX

1.2 Customer Audit Policy:

The Bio Pharma 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.

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 facility to its Stroudsburg facility. The processes were initially validated in the Stroudsburg facility throughout 2000 and 2003. 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

There are five processing rooms and four packaging rooms within BioSpectra's Stroudsburg, PA, 25,000 square foot facility. The warehouse consists of 8,000 square feet of space with a push-back racking system that is capable of storing over 500,000 kg of material. The Quality Control Laboratory consists of 800 square feet of space.

There are approximately 130 employees for BioSpectra sites.

Site Activities Conducted

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

Chemical Manufacturing
Multicompendial Testing
Enzyme Analysis
Wet Chemistry Analysis (If Applicable)
Spectroscopy: UV/VIS, IR
Karl Fisher Titrations
Melting Point Determination
Residue on Ignition
Titrations

1.4 Primary applications of products produced at this site:

At the Stroudsburg, PA site, Bio Pharma Grade Urea is manufactured in accordance with IPEC guidelines and is intended to be used as an excipient for further manufacturing or for research and development.

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

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

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.

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.

Section 2 – Compliance Evidence

2.1 ISO Registration and ISO Certification:

BioSpectra Facilities are not registered with ISO.

2.2 General GMP Statement:

BioSpectra is a cGMP facility with a Quality System created in accordance with IPEC Guidelines. 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 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. 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 and IPEC guidelines to ensure that current good manufacturing practices are followed.

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.

Section 3 – IPEC-PQG GMP Compliance Details:

BioSpectra manufactures Bio Pharma grade products in accordance with IPEC Guidelines.

3.1 Quality Management Systems- 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 IPEC guidelines.
- All responsibilities of the Quality Unit are clearly defined.
- Bio Pharma 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 Pharma Product.

Documentation Requirements

- Documentation rules and standards are defined by BioSpectra's Document Creation in ensur, 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.

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, investigations, internal audits, external audits and batch failures.
- Management provides necessary objectives for appropriate planning of operations for continuous development and growth.

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 training in cGMPs 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), safety glasses, Tyvek Laboratory coats (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.

3.4 Product Realization

Design and Development

- All processes at BioSpectra are developed, qualified and validated for intended use. Dedicated equipment is cleaned and verified in accordance with BioSpectra's cleaning requirements.

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.

3.5 Measurement, Analysis and Improvement

General

- BioSpectra provides complete testing of all products in each phase of manufacturing from raw materials to finished goods. The stability 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 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's Customer 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 guidances.
- All data for testing is recorded directly into permanently bound, sequentially numbered laboratory notebooks using permanent ink. All sample identification information is recorded on sample labels as well as in the laboratory notebooks.
- 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 preparations of solutions.
- USP Traceable Reference Standards are utilized when available Finished Good Testing is performed on every lot of finished product manufactured prior to release. Testing is reviewed by Quality Assurance or a qualified designee 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, 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 are performed to determine the root cause of the nonconformance. Material is completely tested prior to shipment and shipments are not released by the quality unit until all investigations are concluded with a final disposition statement of the product.
- Material may be reprocessed one time, 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 Testing Program.
- Chemicals that are returned to BioSpectra are evaluated for the 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 measureable 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.

SITE AND SUPPLY CHAIN SECURITY OVERVIEW

Section 1 – Scope

1.1 BioSpectra Stroudsburg, PA Facility: 1474 Rockdale Lane, Stroudsburg, PA 18360

1.2 Urea UR4XXX is the only Chemical covered by this Regulatory Datasheet.

Section 2 – Supply Chain Security

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.

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 are issued by the Production Manager and traceability of each seal is evident with a seal accountability form as well as the sequential numbering.

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

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

2.5 Qualification of forwarders/Brokers is not applicable for Urea UR4XXX.

2.6 Qualification of intermediate storage locations is not applicable for Urea UR4XXX.

2.7 Repacking and relabeling activities are not applicable for Urea UR4XXX once it is shipped from a BioSpectra facility.

2.8 Tamper Evidence is apparent using the BioSpectra sequentially numbered seals.

Section 3 – Safety and Environmental Information

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.

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

3.3 BioSpectra has created an emergency response 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.

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