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TECHNICALLY UNAVOIDABLE PARTICLE PROFILE (TUPP) – UREA

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1. PURPOSE:

- 1.1. The purpose of this document is to provide the user of this product with a Technically Unavoidable Particle Profile (TUPP) for Urea manufactured in Process Suite 4 at BioSpectra's Stroudsburg, PA manufacturing facility.

2. SCOPE:

- 2.1. This TUPP applies to the manufacturing and packaging process of Urea, Excipient, at BioSpectra's Stroudsburg, PA manufacturing facility.

3. REFERENCES:

- 3.1. BSI-DGM-0012, FMEA & CE Matrix Template
- 3.2. BSI-FRM-0501, Contaminant Form
- 3.3. BSI-SOP-0006, Pre-Process Room Inspection SOP
- 3.4. BSI-SOP-0049, Equipment Preventative Maintenance
- 3.5. BSI-SOP-0057, Supplier, Manufacturer, and Service Provider Qualification Master Plan
- 3.6. BSI-SOP-0081, Written and Verbal Complaints
- 3.7. BSI-SOP-0084, Change Control
- 3.8. BSI-SOP-0102, Degradation and Impurity Profiling SOP
- 3.9. BSI-SOP-0137, Discrepancy Investigation Procedure
- 3.10. BSI-SOP-0435, Equipment Qualification Master Plan
- 3.11. IPEC; Technically Unavoidable Particle Profile (TUPP) Guide

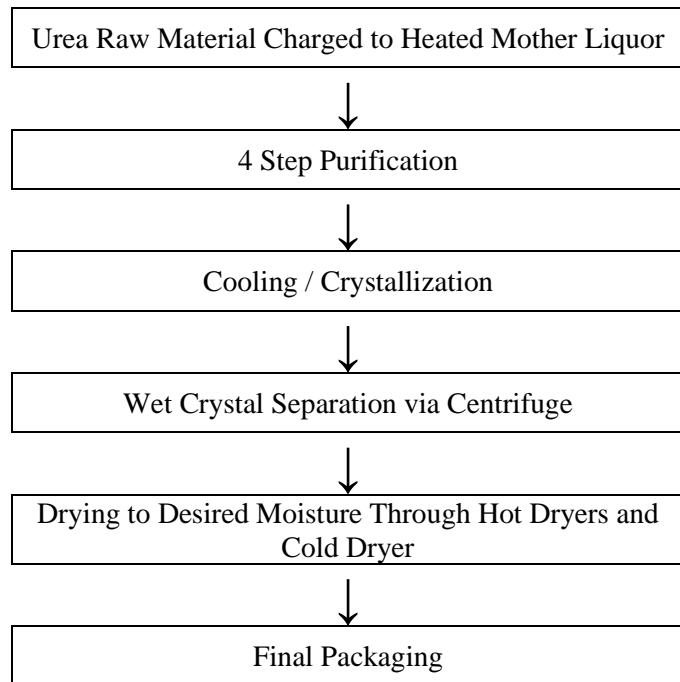
4. DEFINITIONS:

- 4.1. **Atypical Particles**: A visibly different particle that can be viewed with the naked eye, that is not consistent with a Technically Unavoidable Particle Profile (TUPP).
- 4.2. **Contaminant**: A visibly different particle that is not inherent of the process or is considered to be avoidable.
- 4.3. **Technically Unavoidable Particle (TUP)**: A visibly different particle that can be viewed with the naked eye that is inherent to the raw material, manufacturing process or product and does not pose risk to patient safety.
- 4.4. **Technically Unavoidable Particle Profiles (TUPPs)**: A report on all potential known Technically Unavoidable Particles (TUP) for an API or below grade process that can be shared with a customer or end user.
- 4.5. **Typical Levels**: Historical particulate levels seen in (product) produced at BioSpectra's Stroudsburg, PA facility and repackaged at BioSpectra's Bangor, PA facility that has been deemed as acceptable. If historical particulate levels are unavailable, then each particle will be classified utilizing a risk-based approach until a typical level can be established.
- 4.6. **Typical Sizes**: Historical particle sizes seen in (product) produced at BioSpectra's Stroudsburg, PA facility and repackaged at BioSpectra's Bangor, PA facility. If historical particulate sizes are unavailable, then the lowest insoluble matter specification will be utilized as the maximum allowable particulate size.

5. TECHNICALLY UNAVOIDABLE PARTICLES (TUP):

- 5.1. Technically unavoidable particles that may be present in GMP processes producing API Finished Goods or below are investigated and assessed to ensure there is no risk to the quality of the finished good material. This report is not applicable to objectionable particles resulting from contamination or adulteration.
- 5.2. Particles typically described as Technically Unavoidable Particles:
 - 5.2.1. A study should be initiated into the raw material, manufacturing, and packaging processes to identify particles.
 - 5.2.1.1. Charred Particles:
 - 5.2.1.1.1. Discolored due to heat or friction.
 - 5.2.1.2. Materials of Construction (MOC):
 - 5.2.1.2.1. From manufacturing equipment that is product contacting or known to have normal and expected wear.
 - 5.2.1.2.2. From packaging components.
 - 5.2.1.2.3. Documented Risk Assessments for these are available in the associated FMEA.
 - 5.2.1.3. Routinely used gaskets, seals, filters, etc.
 - 5.2.1.3.1. Expected to have normal wear.
 - 5.2.1.4. Lubricants, greases, oils or like materials.
 - 5.2.1.4.1. Discolored due to traces of such materials.
 - 5.2.1.4.2. Should be approved for use as food grade or food contact grade or justified otherwise.
 - 5.2.1.5. Misshapen or morphologically distinct particles.
 - 5.2.1.5.1. Compressions/agglomerations, elongated/tangles, or flakes.
 - 5.2.1.6. Color variation inherent of the product.
 - 5.2.1.7. Intrinsic components carried through from raw materials.
 - 5.2.1.7.1. Mined or sourced from natural products.
- 5.3. The construction of a technically unavoidable particle profile assumes that GMPs are followed and possible mitigation strategies are taken, the remaining particles, if they pose no risk to safety, are deemed technically unavoidable.
- 5.4. Technically unavoidable particles could originate from any of the following parts of the manufacturing process: material of construction of the manufacturing equipment that is product contacting, consumable process equipment, material of construction of the packaging components and any materials that are involved in the manufacturing process that may come into contact with the product that are the lowest risk scenarios.

6. PROCESS FLOW DIAGRAM:



7. PROFILE:

7.1. Manufacturing Location:

7.1.1. Process Suite 4 at BioSpectra's Stroudsburg, PA manufacturing facility

7.2. Applicable Product Codes:

7.2.1. All Urea excipient and below product codes

7.3. TUPPs originating from product contacting surfaces in the manufacturing process:

Table 1: Originating from the S04 Process Suite

Identity	Characterization	Origin	How Removed	How Prevented	Picture	Typical Sizes	Typical Levels
Cellulose	Fiber	Filtration (Filter media)	4-Step Purification, Reprocessing	Replacement of Filters, Inspection		≤1MM	Not Expected - Low Level
Silica	White Powder	Filtration (Filter media)	4-Step Purification, Reprocessing	Replacement of Filters, Inspection		≤1MM	Not Expected - Low Level
Carbon	Black particle	Filtration (Filter media), Centrifugal Pump, Shaft Seal, Tank agitator seals	4-Step Purification, Reprocessing	Replacement of Filters, Inspection		≤0.05MM	Not Expected - Low Level
PTFE	White Plastic	Filter Gaskets, Sanitary Piping Gaskets, Centrifuge Gaskets	4-Step Purification, Reprocessing	Replacement of Filters, Pre-Process Inspection, Preventative Maintenance		≤2MM	Not Expected - Low Level
Silicon Carbide	Ceramic Fragment	Centrifugal Pump Stationary Seat	4-Step Purification, Reprocessing	Pre-Process Inspection, Preventative Maintenance		≤0.05MM	Not Expected - Low Level
Viton	Black elastomer fragment	Pumps (O-rings, gaskets), Process piping gaskets	4-Step Purification, Inspection of the Product, Reprocessing	Pre-Process Inspection, Preventative Maintenance		≤1MM	Not Expected - Low Level
Neoprene	White Elastomer	Siever (Gaskets)	Not Applicable	Pre-Process Inspection, Preventative Maintenance		≤1MM	Not Expected - Low Level

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Identity	Characterization	Origin	How Removed	How Prevented	Picture	Typical Sizes	Typical Levels
FEP	White Plastic	Process Hose Lining	4-Step Purification, Inspection of the Product, Reprocessing	Pre-Process Inspection, Preventative Maintenance	Not Applicable	$\leq 1\text{MM}$	Not Expected - Low Level
Poly-propylene	Natural colored opaque, opaque off-white plastic	ML Return Tank, Process Piping, Vacuum Conveyor Hopper	4-Step Purification, Inspection of the Product, Reprocessing	Pre-Process Inspection, Preventative Maintenance		$\leq 2\text{MM}$	Not Expected - Low Level
PVC	White, Clear, Opaque plastic	ML Tote Process hose (Fittings), Centrifuge ML Return Hose, Dryer Exhaust Duct, Process Piping, Vacuum Conveyor Hose, Centrifuge Wash, Tank Piping	4-Step Purification, Inspection of the Product, Reprocessing	Pre-Process Inspection, Preventative Maintenance		$\leq 2\text{MM}$	Not Expected - Low Level
Silicone	Clear polymer, Orange elastomer fragment	Piping Gaskets, Dryer Bed Gaskets	Inspection of the Product, Reprocessing, 4-step Purification	Pre-Process Inspection, Preventative Maintenance		$\leq 1\text{MM}$	Not Expected - Low Level
Stainless Steel 316	Metallic shaving	Vacuum Conveyor, Hopper, Agitator (Body of Unit), Portable Sprayer (Vessel), Filter Housing, Piping, Tank Agitators (Body of Unit), Wash Tank (Vessel), Centrifugal Pump (Housing), Centrifuge (Body of Unit), Fluid Bed Dryer (Body of Unit), Hot/Cold Tanks (Vessel)	4-Step Purification, Inspection of the Product, Reprocessing	Pre-Process Inspection, Preventative Maintenance		$\leq 0.05\text{MM}$	Not Expected - Low Level

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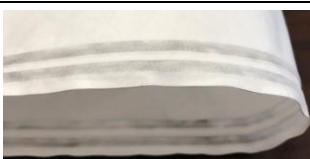
Identity	Characterization	Origin	How Removed	How Prevented	Picture	Typical Sizes	Typical Levels
Stainless Steel 304	Metallic shaving	Siever	Inspection of the Product, Reprocessing	Pre-Process Inspection, Preventative Maintenance		≤0.05MM	Not Expected - Low Level
Tygon	Clear Elastomer	ML Pump Tubing	4 Step Purification	Pre-Process Inspection, Preventative Maintenance		≤1MM	Not Expected - Low Level
Poly-carbonate	Clear Plastic	Piping Sight Glass, Dryer Sight Glass, Cyclone	4-Step Purification, Inspection of the Product, Reprocessing	Pre-Process Inspection, Preventative Maintenance	Not Available	≤2MM	Not Expected - Low Level
HDPE	White HDPE	Centrifuge flange spacer, Vacuum Conveyor Hopper	4-Step Purification, Inspection of the Product, Reprocessing	Pre-Process Inspection, Preventative Maintenance		≤2MM	Not Expected - Low Level
CPVC	Gray Plastic	Filter Housing Piping	4 Step Purification	Pre-Process Inspection, Preventative Maintenance		≤2MM	Not Expected - Low Level
Vinyl plastic	Blue	Sanitary fitting cover	Inspection at time of use	Inspection at time of use		≤2MM	Not Expected - Low Level

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7.4. TUPPs originating from product contacting surfaces of the packaging components:

7.4.1. The following TUPPs are dependent on the packaging type.

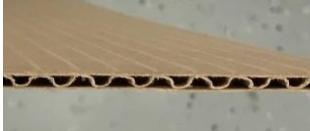
Table 2: Originating from product contacting surfaces of the packaging components

Identity	Characterization	Origin	How Removed	How Prevented	Picture
Hexene LLDPE	Clear plastic	Poly Liner	Reprocessing	Inspection at time of use	
Tyvek	White Plastic	Tyvek Liner	Reprocessing	Inspection at time of use	
HDPE	White Plastic	Bottle and Lid (Packaging)	Reprocessing	Inspection at time of use	

7.5. Atypical particles originating from non-product contacting surfaces of the packaging components:

7.5.1. The following Atypical particles are dependent on the packaging type.

Table 3: Originating from non-product contacting surfaces of the packaging

Identity	Characterization	Origin	How Removed	How Prevented	Picture
HMW-HDPE	Blue Plastic	Drum (Packaging)	Reprocessing	Inspection at time of use	
HDPE	Blue or White Plastic	Pail and Lid (Packaging)	Reprocessing	Inspection at time of use and Product Care Procedure	
Fiber	Brown cardboard	Drum (Packaging) Drum (Desiccant Storage)	Reprocessing	Inspection at time of use	
Cardboard	Brown	Pallet Liner	Reprocessing	Inspection at time of use	
Wood	Wood Shaving	Pallet	Reprocessing	Inspection at time of use	

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7.6. Atypical particles originating from personal protective equipment (PPE) or manufacturing uniforms:

Table 4: Originating from PPE/Uniforms

Identity	Characterization	Origin	How Removed	How Prevented	Picture	Typical Sizes	Typical Levels
Nitrile	Blue	Gloves	Inspection at time of use	Inspection at time of use		≤2MM	Not Expected – Low Level
Tyvek	White	Disposable Lab Jackets, Coveralls, PAPRs and Sleeves	Inspection at time of use	Inspection at time of use		≤2MM	Not Expected – Low Level
Polyester	Blue and Black Fibers	Manufacturing Uniform and PAPRs	Inspection at time of use	Inspection at time of use		≤2MM	Not Expected – Low Level